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File 351:DERWENT WPI 1963-1999/UD=9913;UP=9913;UM=9913
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Set	Items	Description
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DIALOG(R)File 351:DERWENT WPI

007985039
WPI Acc No: 89-250151/198935
XRAM Acc No: C89-111401
new N-piperidinylalkyl- arylalkene-amide derivs. - useful as cholinesterase antagonists and cerebral function improvers
Patent Assignee: TAKEDA CHEM IND LTD (TAKE)
Inventor: GOTO G; NAGAOKA A
Number of Countries: 016 Number of Patents: 007
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
EP 330026	A	19890830	EP 89102376	A	19890211		198935 B
JP 2138255	A	19900528	JP 8926260	A	19890203		199027
US 5169856	A	19921208	US 89306579	A	19890206	A61K-031/445	199252
EP 330026	B1	19941005	EP 89102376	A	19890211	C07D-211/26	199438
DE 68918609	E	19941110	DE 618609	A	19890211	C07D-211/26	199444
			EP 89102376	A	19890211		
CA 1339895	C	19980602	CA 590959	A	19890214	C07D-211/34	199833
JP 2832979	B2	19981209	JP 8926260	A	19890203	C07D-211/26	199903

Priority Applications (No Type Date): JP 88114169 A 19880511; JP 8832339 A 19880215; JP 8926260 A 19890203
Cited Patents: EP 229391; 2.Jnl.Ref
Patent Details:

Patent	Kind	Lan	Pg	Filing Notes	Application	Patent
EP 330026	A	E	19			
Designated States (Regional): AT BE CH DE ES FR GB GR IT LI LU NL SE						
US 5169856	A		12			
EP 330026	B1	E	44			
Designated States (Regional): AT BE CH DE ES FR GB GR IT LI LU NL SE						
DE 68918609	E			Based on		EP 330026
JP 2832979	B2		18	Previous Publ.		JP 2138255

Abstract (Basic): EP 330026 A
Piperidine derivs. of formula (I) and their salts are new; where ring A = opt. substd. aromatic ring; R1 = H; opt. substd. hydrocarbyl; or completes an opt. substd. carbocyclic gp. together with the CH=CH gp. and 2C from ring A; R2 = H, opt. substd. hydrocarbyl or opt. substd. acyl, R3 = opt. substd. hydrocarbyl; n = 2-6.

USE - (I) are cholinesterase antagonists and also improve cerebral functions. (I9 can be used to treate e.g. senile dementia, Alzheimers diseases, Huntington's chorea, hyporkinesos and menia. Dose is 0.001-100

Abstract (Equivalent): EP 330026 B

A compound of the formula (I) wherein ring A stands for a benzene, naphthalene, anthracene or 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from nitrogen atom, oxygen atom and sulphur atom which may be substituted with one to four substituents selected from the group consisting of a C1-4 alkyl, a halogen atom, nitro, cyano, hydroxy, a C1-4 alkoxy, a C1-4 alkylthio, amino, a mono- or di-C1-4 alkyl-substituted amino, C1-4 alkylcarbonylamino, C1-4 alkylsulphonylamino, C1-4 alkoxycarbonyl, hydroxycarbonyl, C1-6 alkylcarbonyl, carbamoyl, mono- or di-C1-4 alkyl-substituted carbamoyl, C1-6 alkylsulphonyl, phenyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl C1-4 alkylcarbamoyl, phenylcarbamoyl, phenyl C1-4 alkylcarbonylamino, benzoylamino, phenyl-C1-4 alkylsulphonyl, phenylsulphonyl, phenyl C1-4 alkylsulphonylamino and phenylsulfonylamino group, wherein the phenyl group or moiety may be further substituted by one or two selected from a C1-4 alkyl group, halogen, hydroxy, benzyloxy, amino, mono- or di-C1-4 alkyl-substituted amino, nitro and C1-4 alkoxycarboxy groups; R1 stands for a hydrogen atom or a straight-chain or branched alkyl groups of 1 to 11 carbon atom, straight-chain or branched C2-4 alkenyl, C2-4 alkynyl, C3-7 monocyclic cycloalkyl, bicyclo(3,2,1)oct-2-yl, bicyclo(3,3,1)-non-2-yl, adamantan-1-yl, phenyl or naphthyl group which may be substituted with 1 to 3 selected from a halogen, nitro, nitrile, hydroxy, C1-4 alkoxy, C1-4 alkylthio, amino, mono or di-C1-4 alkyl substituted amino, C1-4 alkoxycarbonyl, hydroxycarbonyl C1-6 alylcarbonyl, carbamoyl, mono- or di-C1-4 alkyl substituted carbamoyl, phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C1-4 alkylcarbamoyl, phenyl carbamoyl and adamantan-1-yl wherein the phenyl group can optionally have 1 to 4 substituents selected from a C1-4 alkyl group, halogen, hydroxy, benzyloxy, amino, mono- or di-C1-4 alkyl-substituted amino, nitro and C1-4 alkoxycarbonyl, or together with the adjacent group -CH=C- and two carbon atoms constituting the ring A, forms 1,2-dihydronaphthalene, 6,7-dihydro-5H-benzocyclohepte ne, 5,6,7,8-tetra-hydrocyclooctene, 4,5-dihydrobenzo(b)thiophene, 4,5-dihydroisobenzofuran, 7,8-dihydro-quinoline or 7,8-dihydroisoquinoline which may be substituted with 1 to 3 selected from a C1-4 alkyl group, halogen, hydroxyl group, C1-4 alkyloxy group, amino, mono- or di-C1-4 alkylsubstituted amino, nitro, cyano and C1-4 alkoxycarbonyl; R2 stands for (i) a hydrogen atom, (ii) a straight-chain or branched alkyl groups of 1

(Dwg.0/0)

Abstract (Equivalent): US 5169856 A

Piperidinoalkyl derivs. of formula (I) and their salts are new. In the formula A is an opt. substd. benzene, naphthalene, anthracene, thiophene, furan, pyrazole, thiazole, isothiazole, noxazole, isoxazole, imidazole, triazole, tetrazole, pyridine, pyrimidine or pyridazine ring; R1 is e.g. H, opt. substd. 1-11C alkyl, 2-4C alkenyl 2-4C alkynyl, 3-7C monocycloalkyl, 8-14C bicycloalkyl, adamantyl, phenyl naphthyl; or R1+CH=C form a carbocyclic ring of formula (a) is 1-3; R2 is e,.g. H or opt. substd. 1-11C alkyl, naphthyl sulphonyl, 1-6C alkoxy carbonyl etc.; R3 is phenyl, naphthyl or phenyl (1-3C) alkyl; and n is

2-6. (E)-3-phenyl-N-(2-C1-benzyl piperidin-4-yl) ethyl)-2-propenamide is specifically claimed.

USE/ADVANTAGE - Anticholinesterase agents active in CNS system for treatment and prevention of e.g. senile dementia, Alzheimer's disease, Huntington's chorea and for improving cerebral function. (I) have lower toxity compared to known cpds..

(Dwg.0/0)

Title Terms: NEW; N; PIPERIDINYL; ALKYL; ARYL; ALKENE; AMIDE; DERIVATIVE; USEFUL; CHOLINESTERASE; ANTAGONIST; CEREBRAL; FUNCTION; IMPROVE

Derwent Class: B03

International Patent Class (Main): A61K-031/445; C07D-211/26; C07D-211/34

International Patent Class (Additional): A61K-031/44; C07D-401/12; C07D-405/12; C07D-407/12; C07D-409/12; C07D-413/12; C07D-417/12; C07D-231-00; C07D-211-00; C07D-213-00; C07D-215-00; C07D-217-00; C07D-233-00; C07D-239-00

File Segment: CPI

Manual Codes (CPI/A-N): B07-D05; B12-C10; B12-G01B3; B12-G04A

Chemical Fragment Codes (M2):

01 C316 D010 D020 D022 D040 D111 D300 D622 D632 F010 F011 F012 F013 F014 F019 F020 F021 F111 F112 F113 F211 F212 F213 F431 F432 F433 F499 F511 F512 F513 F521 F522 F523 F530 F541 F542 F543 F570 F610 F620 F710 F720 G001 G002 G003 G010 G013 G015 G019 G020 G021 G022 G029 G030 G031 G032 G039 G040 G050 G051 G060 G100 G111 G112 G113 G211 G221 G222 G230 G240 G299 G331 G530 G543 G553 G563 G573 G583 G599 G640 G699 G740 G799 H100 H101 H102 H103 H121 H122 H123 H141 H142 H143 H161 H162 H163 H181 H182 H183 H2 H201 H321 H322 H323 H341 H342 H343 H361 H362 H363 H381 H382 H383 H401 H402 H403 H404 H405 H441 H442 H443 H444 H461 H462 H463 H464 H481 H482 H483 H484 H521 H522 H523 H541 H542 H543 H561 H562 H563 H581 H582 H583 H584 H592 H594 H596 H598 H599 H600 H602 H603 H604 H608 H609 H621 H622 H623 H641 H642 H643 H661 H662 H663 H681 H682 H683 H684 H685 H686 H689 H713 H714 H716 H721 H722 H723 H724 H731 H732 J011 J012 J013 J014 J111 J112 J113 J131 J132 J133 J211 J212 J231 J232 J241 J252 J271 J272 J273 J311 J312 J321 J322 J331 J332 J341 J342 J351 J352 J361 J371 J372 J373 J521 J522 J523 J581 J582 J583 K351 K353 K399 K442 K499 L142 L143 L144 L145 L199 L410 L431 L463 L532 M111 M112 M113 M114 M115 M116 M119 M121 M122 M123 M124 M125 M126 M129 M131 M132 M133 M136 M139 M141 M142 M143 M147 M149 M150 M210 M211 M212 M213 M214 M215 M216 M220 M221 M222 M223 M224 M225 M231 M232 M233 M240 M262 M271 M272 M273 M280 M281 M282 M283 M311 M312 M313 M314 M315 M316 M321 M322 M323 M331 M332 M333 M334 M340 M342 M343 M344 M349 M352 M362 M371 M372 M373 M381 M383 M391 M392 M393 M412 M413 M510 M511 M521 M522 M530 M531 M532 M533 M540 M541 M542 M543 M630 M640 M650 M710 M903 M904 P446 P616 V813 8935-04101-N 00061 00094 00096 00417 01755 01861 01904 03624

02 G013 G100 K0 K4 K431 M210 M211 M240 M281 M320 M414 M510 M520 M531 M540 M730 M903 M910 Q421 00061 00094 00096 00417 01755 01861 01904 03624

Ring Index Numbers: 00061; 00094; 00096; 00417; 01755; 01861; 01904; 03624

Derwent Registry Numbers: 0329-S; 0361-S; 0760-S; 1416-S

Generic Compound Numbers: 8935-04101-N

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     $0.60  TYMNET
     $6.52  Estimated cost this search
     $6.60  Estimated total session cost    0.290 DialUnits
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Description

This invention relates to novel unsaturated carboxylic acid amide derivatives useful as Pharmaceuticals, especially as agents for improving cerebral functions in senile dementia, Alzheimer's disease, etc.

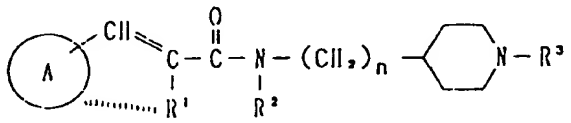
With the increase of aged population, a variety of compounds having actions of improving cerebral functions have been suggested. Among them, physostigmine, an anticholinesterase agent, has been found to have an action of improving cerebral functions.

Physostigmine, however, has such drawbacks as a short duration of action and high toxicity.

EP-A-0 229 391 discloses carboxylic acid amides substituted by piperidylalkyl groups which compounds exhibit dementia preventing activity.

The object of the present invention is to provide compounds with longer action and with lower toxicity, as compared with known compounds improving cerebral functions.

The present inventors succeeded in creating unsaturated carboxylic acid amide derivatives represented by the general formula (I):



(I)

wherein ring A stands for an optionally substituted aromatic ring; R^1 stands for a hydrogen atom or an optionally substituted hydrocarbon group or forms an optionally substituted carbocyclic ring with the adjacent group -CH=C- together with two carbon atoms constituting the ring A; R^2 stands for a hydrogen atom, an optionally substituted hydrocarbon group or an optionally substituted acyl group; R^3 stands for an optionally substituted hydrocarbon group; and n denotes an integer ranging from 2 to 6, or salts thereof, and found that these compounds have a strong cholinesterase antagonizing action as well as a potent action of improving cerebral functions.

The present invention relates to compounds represented by the formula (I) or salts thereof, methods of preparing them and anticholinesterase agents containing them as well as agents containing them for improving cerebral functions.

In the above formula (I), examples of "hydrocarbon group" of "optionally substituted hydrocarbon group" represented by R^1, R^2 and R^3 include those in the form chain-like, cyclic, saturated or unsaturated group and combinations thereof. Examples of chain-like saturated hydrocarbon groups in chain form include straight-chain or branched alkyl groups of 1 to 11 carbon atoms (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, tert-butyl, n-pentyl, n-hexyl).

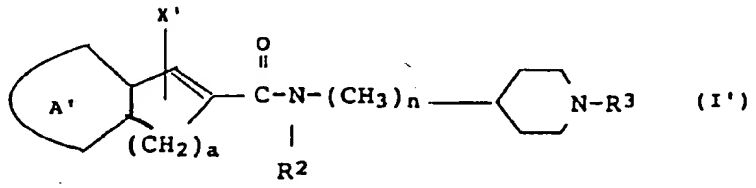
Examples of chain-like unsaturated hydrocarbon groups in chain form include straight-chain or branched C_{2-4} alkenyl e.g. vinyl, allyl, 2-butenyl, and C_{2-4} alkynyl groups (e.g. propargyl, 2-butynyl).

Examples of cyclic saturated hydrocarbon groups include C_{3-7} monocyclic cycloalkyl (e.g. cyclobutyl, cyclopentyl, cyclohexyl), and C_{8-14} cross-linked cyclic saturated hydrocarbons, e.g. bicycloctyls such as bicyclo[3,2,1]oct-2-yl, bicyclononyls such as bicyclo[3,3,1]nonan-2-yl, and tricyclodecyls such as adamantan-1-yl. Cyclic unsaturated hydrocarbon groups include phenyl group, naphthyl group, etc.

Examples of substituents of these hydrocarbon groups include such groups as halogen atoms (e.g. chlorine, bromine, iodine), nitro, nitrile, hydroxy, C_{1-4} alkoxy (e.g. methoxy, ethoxy, propoxy, butyloxy, isopropyloxy), C_{1-4} alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio), amino, mono or di-C_{1-4} alkyl substituted amino (e.g. methylamino, ethylamino, propylamino; dimethylamino, diethylamino), C_{1-4} alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isobutoxycarbonyl), hydroxycarbonyl, C_{1-6} alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, butylcarbonyl, cyclohexylcarbonyl), carbamoyl, mono- or di-C_{1-4} alkyl substituted carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, diethylcarbamoyl, dibutylcarbamoyl), phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl C_{1-4} alkylcarbamoyl and phenyl carbamoyl which may have 1 to 4 substituents and adamantan-1-yl. Substituents on the phenyl groups or naphthyl groups are exemplified by C_{1-4} alkyl groups such as methyl, ethyl, propyl, butyl, isopropyl, etc. The phenyl groups can optionally have 1 to 4 substituents (substituents on the phenyl group are exemplified by C_{1-4} alkyl group such as methyl, ethyl, propyl, butyl, isopropyl, etc., halogen such as chlorine, bromine, iodine, etc., hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro, C_{1-4} alkoxycarbonyl, etc.), halogen such as chlorine,

(e.g. acetylamino, propionylamino, butyrylamino, etc.), C_{1-4} alkylsulfonylamino e.g. methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, etc.), C_{1-4} alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isobutoxycarbonyl, etc.), hydroxycarbonyl, C_{1-6} alkylcarbonyl (e.g. methylcarbonyl, ethylcarbonyl, butylcarbonyl, cyclohexylcarbonyl, etc.), carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, diethylcarbamoyl, dibutylcarbamoyl, etc.), C_{1-6} alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, cyclopentylsulfonyl, cyclohexylsulfonyl, etc.), phenyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl C_{1-4} alkylcarbamoyl, phenylcarbamoyl, phenyl C_{1-4} alkylcarbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl C_{1-4} alkylsulfonylamine and phenylsulfonylamino group, which may have 1 to 4 further substituents. The phenyl groups in these substituents can be further substituted by C_{1-4} alkyl groups such as methyl, ethyl, propyl, butyl, isopropyl, etc., halogen such as chlorine, bromine, iodine, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino such as methylamino, dimethylamino, etc., nitro, C_{1-4} alkoxycarboxy groups. The number of substituents on the ring A is preferably 1 to 3. Ring A is preferably unsubstituted or has one or two of the above substituents.

When R^1 forms an optionally substituted carbocyclic ring with the adjacent group -CH = C- together with two carbon atoms constituting the ring A, compound (I) can be represented by the formula (I'):



wherein A' is a ring defined in the same way as ring A above; X' is hydrogen, C_{1-4} alkyl, halogen, hydroxy, C_{1-6} alkoxy, amino, mono- or di-C_{1-4} alkylamino, cyano or C_{1-4} alkoxycarbonyl etc.; a is an integer from 1 to 3, and other the symbols are defiend above.

Referring to preferable embodiments of the compounds shown by the above formula (I), as the ring A, benzene, pyridine, furan and thiophene can be used, and benzene and pyridine are especially preferable.

Preferable examples of R^1 include a hydrogen atom, C_{1-6} alkyl group such as methyl, ethyl, propyl, etc., a substituted or unsubstituted phenyl group, or R^1 can also preferably be a group forming 1,2-dihydronaphthalene or 6,7-dihydro-5H-benzocycloheptane together with the adjacent group -CH = C- and two carbon atoms of the ring A. Especially preferred R^1 is a hydrogen atom or phenyl or where 6,7-dihydro-5H-benzocycloheptene is formed in combination with the adjacent double bonded group -CH = C-and the ring A.

Preferable examples of R^2 include a hydrogen atom, C_{1-6} alkyl such as methyl, ethyl, propyl, etc., optionally substituted phenyl, C_{1-6} alkylcarbonyl such as acetyl, propionyl, butyryl, etc. or arylcarbonyl such as benzoyl, especially hydrogen atom, C_{1-6} alkylcarbonyl or benzoyl.

As R^3, an optionally C_{1-3} alkyl substituted aromatic hydrocarbon, e.g. phenyl, naphthyl or phenyl-C_{1-3} alkyl can be used, benzyl is especially preferred.

Preferable examples of the substituents (X) on the ring A include a C_{1-4} alkyl group such as methyl, ethyl, propyl, etc., halogen atom such as chlorine, bromine, etc., nitro, cyano, a C_{1-4} alkoxy group such as methoxy, ethoxy, propyloxy, etc., an optionally substituted phenoxy C_{1-4} alkylcarbonylamino such as acetylamino, propionylamino, C_{1-4} alkylsulfonylamino such as methylsulfonylamino, ethylsulfonylamino, etc., phenyl C_{1-4} alkylsulfonylamino such as benzylsulfonylamino, etc., optionally substituted phenylsulfonylamino, C_{1-4} alkylcarbonyl such as acetyl, propionyl, butyryl, etc., C_{1-4} alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, butoxycarbonyl, etc., optionally substituted phenoxycarbonyl, optionally substituted benzoyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl such as methylcarbamoyl, ethylcarbamoyl, butylcarbamoyl, etc., optionally substituted phenylcarbamoyl, optionally substituted C_{1-6} alkylthio such as methylthio, ethylthio, propylthio, etc., optionally substituted phenyl-C_{1-4} alkylthio such as benzylthio, phenethylthio, etc., optionally substituted C_{1-6} alkylsulfinyl such as metylsulfinyl, ethylsulfinyl, propylsulfinyl, etc., optionally substituted phenyl-C_{1-4} alkylsulfinyl such as benzylsulfinyl, phenethylsulfinyl, etc., C_{1-6} alkylsulfonyl such as methylsulfonyl, propylsulfonyl, cyclohexylsulfonyl, etc., optionally substituted phenyl-C_{1-4} alkylsulfonyl, phenyl-C_{1-4} alkyl such as optionally substituted phenylsulfonyl, optionally substituted phenyl, phenyl-C_{1-4} alkyl such as optionally substituted benzyl, etc. Among them, C_{1-4} alkyl, halogen nitro, cyano, acetylamino, C_{1-4} alkoxy, optionally substituted phenyl, optionally substituted benzyl,

optionally substituted benzoyl, optionally substituted benzoylamino, optionally substituted C_{1-6} alkylsulfonyl, optionally substituted benzylsulfonyl, optionally substituted phenylsulfonylamino, optionally substituted benzylsulfonylamino, optionally substituted phenylcarbamoyl, methoxycarbonyl, diethoxycarbonyl, etc. are especially preferable.

The substituent X on ring A which contains a phenyl group therein is referred to herein also as group Q. Thus, group Q includes a phenyl, benzyl, benzoyl, benzoylamino, benzylsulfonyl, phenylsulfonylamino, benzylsulfonylamino, or phenylcarbamoyl etc. The group Q may be optionally substituted with 1 to 3 of C_{1-4} alkyl, phenyl, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkylamino, nitro or C_{1-4} alkoxycarbonyl etc.

As X, electron attractive groups are especially preferable among the above-mentioned groups.

The ring having no substituent is also preferable.

As n are preferable 2,3 and 4.

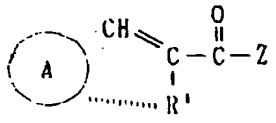
Especially preferred are compounds (I) wherein the ring A is benzene or pyridine; R^1 is a hydrogen atom, methyl or phenyl group or forms 6,7-dihydro-5H-benzocycloheptene or 1,2-dihydronaphthalene together with the adjacent group -CH = C- and the ring A; R^2 is an acetyl or propionyl group, R^3 is a benzyl group; n is 2, 3 or 4; and the ring A is unsubstituted or substituted with a nitro group or acylamino group.

The compound (I) of the present invention may form an acid addition salt, especially a physiologically acceptable acid addition salt. As these salts, mention is made of, for example, salts with an inorganic acid (e.g. hydrochloric acid, nitric acid, phosphoric acid, hydrobromic acid, sulfuric acid) or with an organic acid (e.g. acetic acid, formic acid, propionic acid, fumaric acid, maleic acid, succinic acid, tartaric acid, citric acid, maleic acid, ascorbic acid, oxalic acid, benzoic acid, methansulfonic acid, benzenesulfonic acid). When the object compound (I) has an acid group such as -COOH, the object compound (I) may form a salt with an inorganic base such as sodium, potassium, calcium, magnesium, ammonia, etc. or an organic base such as trimethylamine, etc.

In the following, the method of producing the object compound (I) is described.

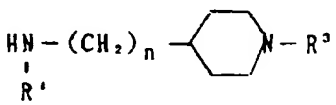
The following explanation is applicable not only to the basic compound (I) per se [including a compound usable as the starting compound for preparing another compound included in the definition of compound (I)], but also the salts thereof mentioned above, and, in the following explanation, these compounds are simply referred to as compound (I).

The compound (I) can be produced by allowing, for example, a compound represented by the formula (II):



(II)

wherein Z stands for a hydroxyl group or a reactive group of carboxylic acid, and other symbols are of the same meaning as defined above, to react with, for example, a compound represented by the formula (III):



(III)

wherein R^4 is the same as R^2, except in the case of optionally substituted acyl, namely, a hydrogen atom or an optionally substituted hydrocarbon residue; R^3 and n are of the same meaning as defined above, or a salt thereof.

As the reactive group of a carboxylic acid represented by Z, mention is made of halogen (e.g. chlorine, bromine, iodine), a lower(C_{1-4}) alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy) and N-hydroxydiacylimidoester (e.g. N-hydroxysuccinic imidoester, N-hydroxyphthalimidoester, N-hydroxy-5-norbornen-2,3-dicarboxyimidoester),etc.

These reactions are carried out usually in an organic solvent such as hydrocarbon (e.g. pentane, hexane, benzene, toluene), halogenated hydrocarbon (e.g. dichloromethane, chloroform, dichloroethane,

carbon tetrachloride), ether (e.g. ethylether, tetrahydrofuran, dioxane, dimethoxyethane), ester (e.g. ethyl acetate, butyl acetate, methyl propionate), amide (e.g. dimethylformamide, dimethylacetamide, hexamethylphosphonotriamide), dimethylsulfoxide, etc., under cooling (-10 °C to 10 °C), at room temperatures (11 °C to 40 °C), or under heating (41 °C to 120 °C), and the reaction time ranges usually from 10 minutes to 12 hours. The amount of the compound (III) is preferably 1.0 to 3.0 equivalents relative to the compound (II). This reaction can be carried out, when desired, for example in the case where Z is hydroxy, in the presence of an acid activating agent such as carbonyldiimidazole, dicyclohexylcarbodiimide, diethyl cyanophosphonate, diphenylphosphorylazide, etc., and, in the case where Z is halogen or lower alkoxy, in the presence of an organic base such as pyridine, 4-dimethylaminopyridine, triethylamine, diisopropylamine, triethylenediamine, tetramethylethylenediamine, etc. or in the presence of an inorganic base such as sodium hydrogen carbonate, potassium hydrogen carbonate, lithium hydrogen carbonate, potassium carbonate, sodium carbonate, lithium carbonate, lithium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydride, etc.

In the case where Z is N-hydroxydiacylimidoester, the reaction is carried out in a solvent, for example, dichloromethane, tetrahydrofuran, dioxane, chloroform, dimethylformamide, acetonitrile, water, etc. This reaction is carried out, when necessary, in the presence of an organic or inorganic base. The reaction temperature ranges usually from -10 °C to 110 °C, preferably from 0 °C to 30 °C, and the reaction time ranges usually from 5 minutes to 12 hours, preferably from 30 minutes to two hours.

A compound of the formula (II) wherein Z is hydroxy [hereinafter abbreviated as compound (II: Z = hydroxy)], i.e. a free carboxylic acid, can be easily prepared by a per se conventional means, for example, by subjecting the compound (II: Z = lower alkoxy), i.e. the ester compound, to hydrolysis with an alkali metal hydroxide (e.g. potassium hydroxide, lithium hydroxide, sodium hydroxide), an alkali metal carbonate (e.g. potassium carbonate, sodium carbonate, lithium carbonate), mineral acid (e.g. hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, hydroiodic acid), an organic acid (e.g. acetic acid, propionic acid, trifluoroacetic acid, monochloroacetic acid, trichloroacetic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid). For the hydrolysis, any conventional solvent can be employed, for example, water, lower(C_{1-4} alkanols (e.g. methanol, ethanol, propanol, butanol), dioxane, tetrahydrofuran, dimethylformamide, etc. are preferable. The reaction temperature ranges usually from about -10 °C to about 120 °C, preferably from 0 °C to 80 °C. The reaction time ranges usually from 10 minutes to 24 hours, preferably from 30 minutes to 6 hours.

The compound (II: Z = halogen) can be prepared by a per se conventional means, for example, by subjecting carboxylic acid to halogenation using a halogenating agent (e.g. phosphorus oxychloride, phosphorus oxybromide, phosphorus pentachloride, phosphorus pentabromide, thionyl chloride, thionyl bromide, sulfuryl chloride, oxalyl chloride, cyanuric acid chloride, boron tribromide, hydrogen iodide). As acid halides to be obtained by the halogenation are mentioned, for example, acid chloride, acid bromide, acid fluoride and acid iodide, especially acid chloride and acid bromide are preferable.

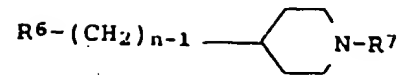
The above-mentioned halogenation is carried out in the absence of solvent or in a conventional solvent. Preferable solvents are, for example, inactive ones such as chloroform, dichloromethane, dichloroethane, benzene, toluene, etc.

The compound (II: Z = hydroxydiacylimidoester) can be prepared by, in a per se conventional manner, allowing the compound (II: Z = hydroxy) to react with an N-hydroxydicarboxylic acid imide (e.g. N-hydroxysuccinic acid imide, N-hydroxyphthalic acid imide, N-hydroxy-5-norbornen-2,3-dicarboxyimide) in the presence of dicyclohexylcarbodiimide. This reaction is carried out in a conventional solvent (e.g. tetrahydrofuran, dioxane, dimethylformamide, acetonitrile, water), and the compound (II: Z = N-hydroxydiacylimidoester) can be fed to the subsequent reaction without isolation thereof.

The compound (II) usable as the starting material can be prepared by a known method or a method analogous thereto. The compound (III) can also be prepared in accordance with a known method or a method analogous thereto.

Among the compounds (III), for example, the compound (III: $R^3 = CH_3Ph$, $R^4 = H$, $n = 2$) (wherein Ph stands for phenyl group, hereinafter the same abbreviation will be applied.) is a known compound, which is disclosed in Synthesis, 388 (1983).

The compound (III) can be prepared by a per se known method by using a known compound represented by the formula(III'):



(III')

wherein $R^6 = CO_2C_2H_5$, $R^7 = CO_2CH_2Ph$, and n = an integer of 2 to 6. For example, the compound (III': $R^6 = CO_2C_2H_5$, $R^7 = CO_2CH_2Ph$, n = integer of 2 to 6) is subjected to catalytic reduction by a conventional method or is treated with an acid to give a compound (III': R^6 and n are of the same meaning as defined above, R^7 = H), to which was then introduced a hydrocarbon residue by a conventional method to give a compound[III': R^6 and n are of the same meaning as above, $R^7 = R^3$ (R^3 is of the same meaning as above)], then the ester group of R^6 is subjected to amidation directly by a conventional means or amidation after converting the ester group of R^6 into a carboxyl group to thereby obtain a compound [III': $R^6 = CONHR^4$, $R^7 = R^3$ (R^3 and n are of the same meaning as defined above)], followed by subjecting the compound to reduction with lithium aluminium hydride by per se conventional means to afford the compound (III).

The above-mentioned known compound, the starting compound, (III':$R^6 = CO_2CH_2H_5$, $R^7 = CO_2CH_2Ph$, n = an integer of 2 to 6) is that disclosed in Japanese Patent Publication (laid open) 99476/1981 and Chem. Pharm. Bull. 34, 3747(1986).

Among the object compounds (I) of the present invention, a compound (I) in which $R^5 = R^2$ (except for the case of R^5 = hydrogen, wherein R^5 is an optionally substituted hydrocarbon residue or acyl group) can also be prepared by introducing hydrocarbon residue into the object compound of this invention (I: $R^2 = H$) or by subjecting the said compound to acylation. For example, the above compound (I: $R^2 = R^5$) can be prepared also by allowing a compound (I: $R^2 = H$) to react with a compound represented by the formula (IV): R^5-Y (wherein R^5 is defined as above; when R^5 is an optionally substituted hydrocarbon residue, Y stands for halogen, and, when R^5 is an optionally substituted acyl group, Y stands for hydroxy, OR^5 or a reactive group of carboxylic acid) by a per se known method.

In the reaction of the compound (I: $R^2 = H$) with a compound (IV), use of a solvent is not always required, and, when required, use of an organic solvent such as hydrocarbon (e.g. pentane, hexane, benzene, toluene), halogenated hydrocarbon (e.g. dichloromethane, chloroform, dichloroethane, carbon tetrachloride), ether (e.g. ethyl ether, tetrahydrofuran, dioxane, dimethoxyethane), amide (e.g. dimethylformamide, hexamethylphosphonotriamide), dimethylsulfoxide, etc. is preferable. The reaction is carried out at temperatures ranging from -10°C to 200°C, preferably from 0°C to 120°C. The reaction time ranges usually from 5 minutes to 12 hours, preferably from 10 minutes to 6 hours. The amount of the above-mentioned compound (IV) is usually equimolar or in an excess relative to the compound (I: $R^2 = H$), preferably 1.1 to 20.0 times as much per mole. When R^5 is an optionally substituted hydrocarbon residue and Y is halogen, the reaction is carried out in the presence of, for example, an organic base such as pyridine, 4-dimethylaminopyridine, triethylamine, diisopropylamine, triethylenediamine, tetramethylethylenediamine, etc. or an inorganic base such as sodium hydride, metallic sodium, potassium amide, sodium hydrogen carbonate, potassium hydrogen carbonate, sodium carbonate, potassium carbonate, lithium hydroxide, potassium hydroxide, sodium hydroxide,etc. The amount of these bases is generally equimolar to excess relative to the compound (II: $R^2 = H$), preferably 1.1 to 5 times as much mol.

And, Examples of the reactive groups of carboxylic acid represented by Y when R^5 stands for an acyl group include halogen (e.g. chlorine, bromine, iodine), lower(C_{1-4}) alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy) and N-hydroxydiacylimidoester (e.g. N-hydroxysuccinic acid imidoester, N-hydroxyphthalic acid imidoester, N-hydroxy-5-norbornene-2,3-dicarboxyimidoester), etc.

And, the reaction of the compound (I: $R^2 = H$) with a compound (IV), when R^5 is an acyl group, can be carried out, if desired, when Y is hydroxy, in the presence of an acid-activating agent such as carbonyldiimidazole, dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphorylazide, etc., when Y is OR^5, in the presence of a mineral acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, etc., an organic acid such as acetic acid, formic acid, propionic acid, methanesulfonic acid, p-toluenesulfonic acid, etc. or an acyl halogenide whose acyl group is the same as R^5, and, when Y is halogen or a lower alkoxy, in the presence of an organic base such as pyridine, 4-dimethylaminopyridine, triethylamine, diisopropylamine, triethylenediamine, tetramethylethylenediamine, etc. or an inorganic base such as sodium hydrogen carbonate, potassium hydrogen carbonate, lithium hydrogen carbonate, lithium hydroxide, potassium hydroxide, sodium hydroxide, etc.

Further, when Y is a N-hydroxydiacylimido ester, the reaction is carried out in a solvent, for example, preferably dichloromethane, tetrahydrofuran, dioxane, chloroform, dimethylformamide, acetonitrile, water, etc. This reaction can be carried out, upon desire, in the presence of an organic or an inorganic base

mentioned above referring to the case where Y is halogen or lower alkoxy.

When the reaction is carried out in the presence of the above-mentioned acid-activating agent, acid, halide and base, the amount of these agents ranges generally from equimolar. to excess relative to the compound (I: $R^2 = H$), preferably in 1.1 to 5 times molar excess.

And, among the object compounds (I) of the present invention, the compound (I: $X = NH_2$) can also be prepared by subjecting also the object compound of the present invention (I: $X = NO_2$) or a salt thereof. The reduction can be conducted by a per se known method, for example those disclosed in J. Am. Chem. Soc., 49 1093(1927) or Ber., 76, 1011(1943) or an equivalent.

This reaction can be carried out, for example, by conducting a catalytic reduction in hydrogen streams, in the presence of a catalyst (e.g. palladium-carbon, platinum dioxide) at normal temperatures under normal pressure. As the solvent, use is made of, for example, methanol, ethanol, water, dimethylformamide, dioxane, etc., but any other solvents can be used so long as they do not inhibit this reaction. This reaction can be carried out, when desired, in the presence of a mineral acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, etc. or an organic acid such as acetic acid, formic acid, propionic acid, oxalic acid, etc.

A compound (I), wherein X stands for an acylamino group (e.g. acetylamino, benzoylamino, benzenesulfonylamino) can be prepared by subjecting a compound (I: $X = NH_2$) to acylation. This acylation can be carried out by allowing the compound (I:$X = NH_2$) to react with an acylating agent, for example, an acid (e.g. acetic acid, propionic acid, benzoic acid, benzenesulfonic acid, p-toluenesulfonic acid), C_{1-4} alkyl ester of an acid (e.g. methyl acetate, ethyl propionate, methyl benzenesulfonate), an acid halogenide (e.g. acetyl chloride, acetyl bromide, p-toluenesulfonic acid chloride, benzenesulfonyl chloride), an acid anhydride (acetic anhydride, propionic anhydride, benzoic anhydride) or N-hydroxydiacylimido ester of an acid (e.g. N-acetyloxysuccinimide, N-benzoyloxyphthalimide, N-acetyloxy-5-norbornene-2,3-dicarboxyimide), etc.

These reactions can usually be carried out in an organic solvent such as hydrocarbon (e.g. pentane, hexane, benzene, toluene), halogenated hydrocarbon (e.g. dichloromethane, chloroform, dichloroethane, carbon tetrachloride), ether (e.g. ethyl ether, tetrahydrofuran, dioxane, dimethoxyethane), ester (e.g. ethyl acetate, butyl acetate, methyl propionate), amide (e.g. dimethylformamide, dimethylacetamide, hexamethylphosphonotriamide), dimethylsulfoxide, etc., under cooling (-10 °C to 10 °C), at room temperatures (11 °C to 40 °C) or under heating (41 °C to 120 °C), and the reaction time ranges from 10 minutes to 12 hours. The amount of the above-mentioned acylating agents ranges preferably from 1.0 to 3.0 equivalents relative to the compound (I: $X = NH_2$). Further, this reaction can be carried out, if desired, when the acylating agent is an acid, in the presence of, for example, an acid-activating agent such as carbonyldiimidazole, dicyclohexylcarbodiimide, diethyl cyanophosphate, diphenylphosphorylazide, etc., and, if the acylating agent is C_{1-4} alkyl ester of an acid or an acid halide, in the presence of an organic base such as pyridine, 4-dimethylaminopyridine, triethylamine, diisopropylamine, triethyleneamine, tetramethylethylenediamine, etc. or in the presence of an inorganic base such as sodium hydrogen carbonate, potassium hydrogen carbonate, lithium carbonate, lithium hydroxide, potassium hydroxide, sodium hydroxide, etc., and, if the acylating agent is an acid anhydride, in the presence of a mineral acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, etc. or an organic acid such as acetic acid, formic acid, propionic acid, methanesulfonic acid, p-toluenesulfonic acid, etc.

Further, if the acylating agent is an N-hydroxydiacylimido ester, the acylation is carried out preferably in the presence of a solvent such as dichloromethane, tetrahydrofuran, dioxane, chloroform, dimethylformamide, acetonitrile, water, etc. This reaction can be carried out, when desired, in the presence of such an organic or inorganic base as mentioned above. The reaction temperature ranges, usually, from -10 °C to 110 °C, preferably from 0 °C to 30 °C, and the reaction time ranges, usually, from 5 minutes to 12 hours, preferably from 30 minutes to 2 hours.

The compound (I) of the present invention acts on the central nervous system of mammals, has a strong anticholinesterase activity and shows an excellent antiamnesic action against various types of induction of amnesia in humans and animals such as mice.

The compound (I) of the present invention has, as compared with physostigmine, such characteristic features as showing a very good separability of the action on the central nerves from that on peripheral nerves, being accompanied with no or very slight actions on peripheral nerves causing convulsion, salivation, diarrhea, in the dosage showing antiamnestic action. The compound (I) has prolonged action and is of low toxicity; it is a remarkably effective by oral administration.

Therefore, the present compounds are useful in agents for improving cerebral functions in a mammal including human beings.

The diseases to which the compounds of the present invention can be effectively applied are senile dementia, Alzheimer's disease, Huntington's chorea, hyperkinesis, mania, etc., and the compounds can be used for the prophylaxis or therapy of these diseases.

The compounds of the present invention can be administered orally or non-orally to mammals including man in various dosage forms such as tablets, granules, capsules, injections, suppositories and so forth. The dose varies with the kinds of deseases, symptoms, etc. Generally, however, in the case of oral administration, the daily dose ranges from 0.001 mg to 100 mg, preferably from 0.01 mg to 10 mg.

The following examples, reference examples, formulation examples and experimental examples are intended to illustrate the present invention in further detail and should by no means be construed as limiting the scope of the present invention.

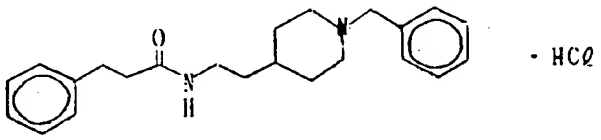
The elution in column chromatography in the examples and reference examples were conducted, unless otherwise specified, using the technique of Thin Layer Chromatography (TLC). The eluate fractions containing the object compound were confirmed and collected by employing, as a supplemental means of detection, the procedure which comprises spraying 48% HBr onto the spot on the TLC plate, hydrolyzing by heating, then spraying thereon a ninhydrin reagent, and heating again to cause change of the color to red to reddish purple. Unless otherwise specified, the silica gel used for the column was Kiesel-gel 60 (70 to 230 mesh) manufactured by E. Merck AG.

The term "room temperatures" usually ranges from about 5 °C to 40 °C.

Unless otherise specified, % means weight percentage.

Example 1

(E)-3-Phenyl-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-propenamide·hydrochloride

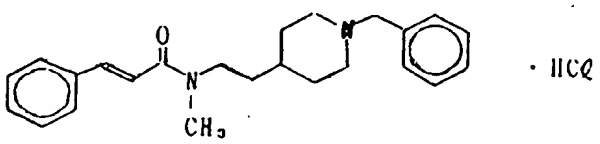


To a dimethylformamide solution (20 ml) containing (E)-cinnamic acid (1.05 g), 4-(2-aminoethyl)-1-benzylpiperidine·dihydrochloride (1.8 g) and triethylamine (1.0 ml) was added, under ice-cooling, diethyl cyanophosphonate (1.7 g). The mixture was stirred for one hour under ice-cooling, and there was added water (100 ml). The mixture was subjected to extraction with dichloromethane. The dichloromethane solution was dried over anhydrous sodium sulfate, then the solvent was distilled off under reduced pressure. The oily residue was subjected to a silica gel column chromatography [developing solvent : ethyl acetate - methanol = 20 : 1(V/V)]. The solvent of the solution containing the object product was distilled off. To the residue was added an ethanolic solution (2.4 ml) of 3N hydrochloric acid, then the solvent was distilled off. The residual solid was recrystallized from ethanol-ether [5:1(V/V)] to give colorless crystals (1.2 g) m.p. 125 to 127 °C.

Elemental Analysis for $C_{23}H_{28}N_2O \cdot HCl$:			
Calcd.	C 71.76	H 7.59	N 7.28
Found	C 71.62	H 7.49	N 7.01

Example 2

(E)-3-Phenyl-N-methyl-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-propenamide•hydrochloride

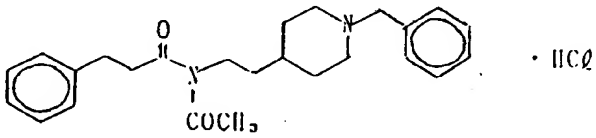


To a dimethylformamide solution (5 ml) of (E)-3-phenyl-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-propenamide•hydrochloride (0.6 g) obtained in Example 1 was gradually added sodium hydride (80 mg) at room temperature and the mixture was stirred at 60 °C for 30 minutes. The reaction mixture was cooled on an ice-bath and there was added methyl iodide (0.21 g), followed by stirring at room temperature for one hour. To the resultant mixture was added water and the mixture was subjected to extraction with dichloromethane. The dichloromethane solution was washed with water and dried over anhydrous sodium sulfate, then the solvent was distilled off. The oily residue was subjected to a silica gel column chromatography [developing solvent : ethyl acetate - methanol = 10 : 1(V/V)]. Then the solvent of the solution containing the object compound was distilled off. To the residue was added an ethanolic solution (0.5 ml) of 3N hydrogen chloride, followed by distilling off the solvent to obtain an amorphous powder (0.2 g).

Elemental Analysis for $C_{24}H_{30}N_2O \cdot HCl$:			
Calcd.	C 72.25	H 7.83	N 7.02
Found	C 72.01	H 7.79	N 6.95

Example 3

(E)-3-Phenyl-N-acetyl-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-propenamide•hydrochloride



(A) A mixture of (E)-3-phenyl-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-propenamide•hydrochloride (0.5 g), acetic anhydride (2.5 ml) and a catalytic amount of p-toluene-sulfonic acid•monohydrate was stirred at 80 °C for 6 hours. The reaction mixture was left standing for cooling, after there was added water. To the mixture was added 10% NaOH to render the pH to about 9 to 10, followed by extraction with dichloromethane. The dichloromethane solution was washed with water and dried over anhydrous sodium sulfate, followed by distilling off the solvent. The oily residue was subjected to a silica gel column chromatography (developing solvent : ethyl acetate). The solvent of the solution containing the object compound was distilled off. To the residue was added an ethanol solution (0.44 ml) of 3N hydrogen chloride, and the solvent was distilled off to obtain a hygroscopic amorphous powder (0.45 g).

Elemental Analysis for $C_{25}H_{30}N_2O_2 \cdot HCl$:			
Calcd.	C 70.32	H 7.32	N 6.56
Found	C 70.18	H 7.29	N 6.41

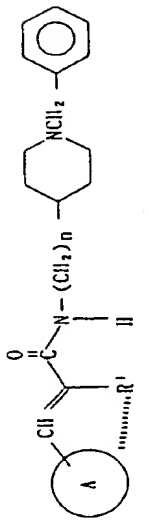
(B) A pyridine solution (5 ml) of (E)-3-phenyl-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-propenamide·hydrochloride (0.25 g) and acetyl chloride (0.3 ml) was stirred at 60°C for 2 hours. Water was added to the reaction mixture after being left standing for cooling; the mixture was dried over anhydrous sodium sulfate. The solvent was distilled off. The oily residue was subjected to silica gel column chromatography (developing solvent : ethyl acetate). The solvent of the solution containing the object compound was distilled off. To the residue was added an ethanol solution of 3N hydrogen chloride. The solvent was then distilled off to obtain hydroscopic amorphous powder (0.16 g).

Elemental Analysis for $C_{25}H_{30}N_2O_2 \cdot HCl$:			
Calcd.	C 70.32	H 7.32	N 6.56
Found	C 70.26	H 7.13	N 6.48

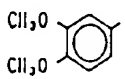
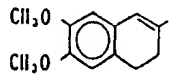
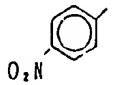
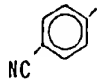
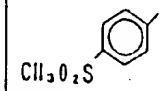
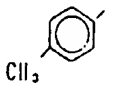
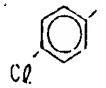
Example 4

By the procedure of Example 1, compounds as set forth in Table 1 were obtained.

Table 1



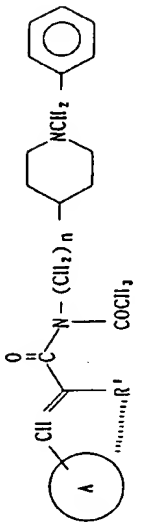
Compound No.	A	R1	n	m.p. (°C)	Molecular Formula	Elemental Analysis Calcd. (Found)		
						C	H	N
1		CH_3	2	amorphous	$C_{24}H_{30}N_2O{\cdot}HCl$	72.25 (72.18	7.83 7.74	7.02 6.98)
2		C_6H_5	2	amorphous	$C_{29}H_{32}N_2O{\cdot}HCl$	75.55 (75.48	7.21 7.11	6.08 6.00)
3		H	2	113 - 115	$C_{29}H_{27}N_3O$	75.61 (75.52	7.79 7.72	12.02 11.96)
4		H	2	180 - 183	$C_{21}H_{26}N_2O_2{\cdot}HCl$	67.28 (67.27	7.26 7.11	7.47 7.39)
5		H	2	89 - 92	$C_{21}H_{26}N_2OS{\cdot}HCl$	64.51 (64.44	6.96 6.93	7.17 7.01)

Compound No.	A	R^1	n	m.p. (°C)	Molecular Formula	Elemental Analysis Calcd. (Found)		
						C	H	N
6		H	2	amorphous	$C_{25}H_{32}N_2O_3 \cdot HCl$	67.48 (67.32	7.47 7.45	6.30 6.27)
7			2	amorphous	$C_{27}H_{34}N_2O_3 \cdot HCl$	68.85 (68.81	7.49 7.45	5.95 5.86)
8		H	2	amorphous	$C_{23}H_{27}N_3O_3 \cdot HCl$	64.25 (64.11	6.56 6.42	9.77 9.61)
9		H	2	amorphous	$C_{24}H_{27}N_3O \cdot HCl$	70.32 (70.14	6.88 6.83	10.2 10.01)
10		H	2	158 - 160	$C_{24}H_{30}N_2O_3S$	67.58 (67.39	7.09 6.98	6.57 6.43)
11		H	2	amorphous	$C_{24}H_{30}N_2O \cdot HCl$	72.25 (72.06	7.83 7.77	7.02 6.93)
12		H	2	108 - 110	$C_{23}H_{27}ClN_2O$	72.14 (72.03	7.11 6.99	7.32 7.03)

Example 5

By a procedure similar to that of Example 3, compounds as set forth in Table 2 were obtained.

Table 2



Compound No.	A	R^1	n	m.p. (°C)	Molecular Formula	Elemental Analysis Calcd. (Found)		
						C	H	N
1		CH_3	2	amorphous	$C_{26}H_{32}N_2O_2 \cdot HCl$	70.81 (70.67	7.54 7.50	6.35 6.29)
2		C_6H_5	2	amorphous	$C_{37}H_{34}N_2O_2 \cdot HCl$	74.01 (73.94	7.01 6.99	5.57 5.54)

Formulation Example 1

(1)	(E)-3-phenyl-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-propenamide•hydrochloride	1 g
(2)	lactose	197 g
(3)	corn starch	50 g
(4)	magnesium stearate	2 g

The above ingredients (1), (2) and corn starch (20 g) were mixed. The mixture was granulated with a paste from corn starch (15 g) and water (25 ml). To the granules was added corn starch (15 g), and the mixture was compressed with a tableting machine into 2000 tablets (3 mm diameter), each containing 0.5 mg of (1).

Formulation Example 2

(1)	(E)-3-phenyl-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-propenamide•hydrochloride	2 g
(2)	lactose	196 g
(3)	corn starch	50 g
(4)	magnesium stearate	2 g

The above ingredients (1), (2) and corn starch (20 g) were mixed. The mixture was granulated with a paste prepared from corn starch (20 g) and water (25 ml). To the granules were added corn starch (15 g) and (4), and the mixture was compressed into 2000 tablets (5 mm diameter), each containing 1 mg of (1).

Experimental Example

Cholinesterase activity was measured radiometrically by the method of Johnson and Russell[1]), modified by Kleinberger and Yanal[2]), with a slight modification.

S_1 fraction of the cerebral cortex of male Wistar rats, the enzyme source, was preincubated in a scintillation vial with drugs for 15 min at room temperature, and then [acetyl-^{3}H]-acetylcholine (final 200 μM) was added and incubated further for 30 min. The reaction was terminated by adding solution containing 1 M chloroacetic acid, followed by toluene-based scintillant, and the vials were capped and shaken to transfer the product, [^{3}H]-acetic acid, to toluene phase. Then radioactivity in the toluene phase was counted by liquid scintillation spectrometry. Inhibitory activity of the test drug was expressed by 50%-inhibitory concentration (IC_{50}), which was calculated by linear regression of log-probit transformation of the inhibition curve. By the same method, cholinesterase activity of physostigmine was measured.

1) C. D. Johnson and R. L. Russell (1975) Anal. Biochem. 64, 229-238.
2) N. Kleinberger and J. Yanai (1985) Dev. Brain Res. 22, 113-123.

The results were shown.

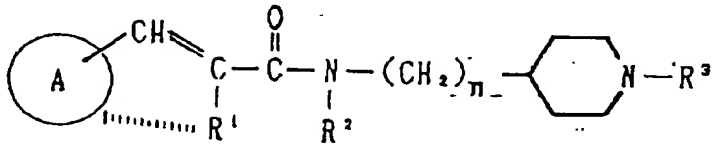
Table 3

Compound (Example No.)	Anti-acetylcholinesterase activity IC_{50} (μM)
1	9.6
2	18
3	0.64
4 - 1	8.1
4 - 2	3.5
4 - 3	2.0
4 - 4	9.9
4 - 5	13
4 - 6	2.6
4 - 7	1.2
4 - 8	2.8
4 - 9	3.3
4 - 10	1.6
4 - 11	15
4 - 12	9.2
physostigmine	0.22

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. A compound of the formula:



wherein ring A stands for a benzene, naphthalene, anthracene or 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom which may be substituted with one to four substituents selected from the group consisting of a C_{1-4} alkyl, a halogen atom, nitro, cyano, hydroxy, a C_{1-4} alkoxy, a C_{1-4} alkylthio,amino, a mono- or di-C_{1-4} alkyl-substituted amino, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonyl, hydroxycarbonyl, C_{1-5} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-5} alkylsulfonyl, phenyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl C_{1-4} alkylcarbamoyl, phenylcarbamoyl, phenyl C_{1-4} alkylcarbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl C_{1-4} alkylsulfonylamine and phenylsulfonylamino group, wherein the phenyl group or moiety may be further substituted by one or two selected from a C_{1-4} alkyl group, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-4} alkoxycarboxy groups; R^1 stands for a hydrogen atom, or a straight-chain or branched alkyl groups of 1 to 11 carbon atom, straight-chain or branched C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} monocyclic cycloalkyl, bicyclo[3,2,1]oct-2-yl, bicyclo[3,3,1]-nonan-2-yl, adamantan-1-yl, phenyl or naphthyl group which may be substituted with 1 to 3 selected from a halogen, nitro, nitrile, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono or di-C_{1-4} alkyl substituted amino, C_{1-4} alkoxycarbonyl, hydroxycarbonyl, C_{1-5} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl substituted carbamoyl, phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkylcarbamoyl, phenyl carbamoyl and adamantan-1-yl wherein the phenyl group can optionally have 1 to 4 substituents selected from a C_{1-4} alkyl group, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-4} alkoxycarbonyl, or together with the adjacent group -CH = C-and two carbon atoms constituting the ring A, forms 1,2-dihydronaphthalene, 6,7-dihydro-5H-benzocycloheptene, 5,6,7,8-tetra-hydrocyclooctene, 4,5-dihydrobenzo[b]thiophene, 4,5-dihydroisobenzofuran, 7,8-dihydro-quinoline or 7,8-dihydroisoquinoline which may be substituted with 1 to 3 selected

from a C_{1-4} alkyl group, halogen, hydroxyl group, C_{1-4} alkyloxy group, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro, cyano and C_{1-4} alkoxycarbonyl; R^2 stands for (i) a hydrogen atom, (ii) a straight-chain or branched alkyl groups of 1 to 11 carbon atom, straight-chain or branched C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} monocyclic cycloalkyl, bicyclo[3,2,1]oct-2-yl, bicyclo[3,3,1]nonan-2-yl, adamantan-1-yl, phenyl or naphthyl group which may be substituted with 1 to 3 selected from a halogen, nitro, nitrile, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono or di-C_{1-4} alkyl substituted amino, C_{1-4} alkoxy-carbonyl, hydroxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl substituted carbamoyl, phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkylcarbamoyl, phenyl carbamoyl and adamantan-1-yl wherein the phenyl group can optionally have 1 to 4 substituents selected from a C_{1-4} alkyl group, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-4} alkoxycarbonyl or (iii) a C_{1-6} alkylcarbonyl, C_{3-8} cycloalkylcarbonyl, C_{3-8} cycloalkyl-C_{1-6} alkylcarbonyl, C_{2-6} alkenyl or alkynylcarbonyl, benzoyl, naphthoyl, carbamoyl, mono- or di-C_{1-4} alkylcarbamoyl, mono- or di-C_{3-6} alkenyl carbamoyl, phenylcarbamoyl, naphthylcarbamoyl, diphenylcarbamoyl, sodium sulfonyl, C_{1-6} alkylsulfonyl, C_{2-6} alkenyl- or alkynyl-sulfonyl, phenylsulfonyl, naphthalenesulfonyl, C_{1-6} alkyloxycarbonyl, C_{3-8} cycloalkyloxycarbonyl, cyclopentylmethyloxycarbonyl, C_{2-7} alkenyl- or alkynyloxycarbonyl, phenyloxycarbonyl, or phenyl-C_{1-2} alkoxycarbonyl which may have further 1 to 3 substituents selected from halogen, nitro, nitrile, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono or di-C_{1-4} alkyl substituted amino, C_{1-4} alkoxycarbonyl, hydroxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl substituted carbamoyl, phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkylcarbamoyl, phenyl carbamoyl and adamantan-1-yl, wherein the phenyl group can optionally have 1 to 4 substituents selected from a C_{1-4} alkyl group, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-4} alkoxycarbonyl; R^3 stands for a straight-chain or branched alkyl groups of 1 to 11 carbon atom, straight-chain or branched C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} monocyclic cycloalkyl, bicyclo[3,2,1]oct-2-yl, bicyclo[3,3,1]nonan-2-yl, adamantan-1-yl, phenyl or naphthyl group which may be substituted with 1 to 3 selected from a halogen, nitro, nitrile, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono or di-C_{1-4} alkyl substituted amino, C_{1-4} alkoxycarbonyl, hydroxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl substituted carbamoyl, phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkylcarbamoyl, phenyl carbamoyl and adamantan-1-yl, wherein the phenyl group can optionally have 1 to 4 substituents selected from a C_{1-4} alkyl group, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-4} alkoxycarbonyl; and n denotes an integer ranging from 2 to 6, or salts thereof.

2. A compound according to claim 1, wherein the ring A is benzene.

3. A compound according to claim 1, wherein the ring A is naphthalene or anthracene.

4. A compound according to claim 1, wherein the ring A is a member selected from the group consisting of thiophene, furan, pyrazole, thiazole, isothiazole, oxazole, isoxazole, imidazole, triazole, tetrazole, pyridine, pyrimidine and pyridazine.

5. A compound according to claim 1, wherein the ring A is unsubstituted or substituted with 1 to 3 selected from C_{1-4} alkyl, halogen, nitro, cyano, acetylamino, C_{1-4} alkoxy, benzyl, benzoylamino, C_{1-6} alkylsulfonyl, benzylsulfonyl, phenylsulfonylamino, benzylsulfonylamino, phenylcarbamoyl, methoxycarbonyl and diethoxycarbonyl.

6. A compound according to claim 1, wherein R^1 is hydrogen, C_{1-11} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or C_{3-7} monocyclic cycloalkyl.

7. A compound according to claim 1, wherein R^1 form a 1,2-dihydronaphthalene together with the adjacent group -CH = C- and two carbon atoms constituting the ring A.

8. A compound according to claim 7, wherein the 1,2-dihydronaphthalene formed by the 5- to 7-membered ring and ring A is unsubstituted or substituted with 1 to 3 selected from C_{1-4} alkyl, halogen, C_{1-4} alkoxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro, cyano and C_{1-4} alkoxycarbonyl.

9. A compound according to claim 1, wherein R^2 is hydrogen, C_{1-11} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or C_{3-7} monocyclic cycloalkyl.

10. A compound according to claim 1, wherein n is an integer of 2, 3 or 4.

11. A compound according to claim 1, wherein ring A is benzene, pyridine, furan or thiophene which may be substituted with C_{1-4} alkyl, C_{1-4} alkoxy, nitro, cyano, halogen or/and C_{1-6} alkylsulfonyl; R^1 is hydrogen, C_{1-6} alkyl or phenyl, or forms 1,2-dihydronaphthalene which may be substituted with C_{1-4} alkoxy together with the adjacent group -CH=C- and two carbon atoms of the ring A; R^2 is hydrogen, C_{1-6} alkyl or C_{1-6} alkylcarbonyl; R^3 is benzyl; and n is 2.

12. A compound according to claim 1, wherein ring A is benzene, pyridine, furan or thiophene which may be substituted with C_{1-4} alkoxy; R^1 is hydrogen, C_{1-6} alkyl or phenyl, or forms 1,2-dihydronaphthalene which may be substituted with C_{1-4} alkoxy together with the adjacent group -CH=C- and two carbon atoms of the ring A; R^2 is hydrogen, C_{1-6} alkyl or C_{1-6} alkylcarbonyl; R^3 is benzyl, and n is 2.

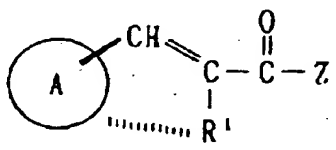
13. A compound according to claim 1, wherein ring A is benzene; R^1 is hydrogen; R^2 is hydrogen, C_{1-6} alkyl or C_{1-6} alkylcarbonyl; R^3 is benzyl; and n is 2.

14. A compound according to claim 1, which is (E)-3-phenyl-N-acetyl-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-propenamide•hydrochloride.

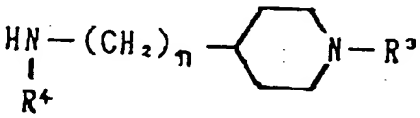
15. A compound according to claim 1, which is (E)-3-(3-pyridyl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2 propenamide.

16. A compound according to claim 1, which is 3,4-dihydro-6,7-dimethoxy-N-[2-(1-benzylpiperidin-4-yl)-ethyl]naphthalene-2-carboxamide•hydrochloride

17. A method of preparing a compound according to claim 1, which is characterized by
(A) allowing a compound represented by a compound represented by the formula:

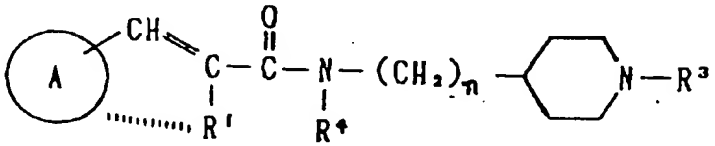


wherein Z stands for a hydroxyl group or a reactive group of carboxylic acid, and other symbols are of the same meaning as defined in claim 1,
to react with a compound represented by the formula:

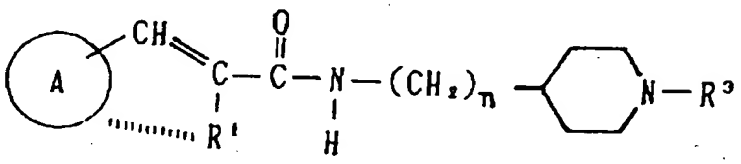


wherein R^4 stands for a hydrogen atom or a straight-chain or branched alkyl groups of 1 to 11 carbon atom, straight-chain or branched C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} monocyclic cycloalkyl, bicyclo[3,2,1]oct-2-yl, bicyclo[3,3,1]nonan-2-yl, adamantan-1-yl, phenyl or naphthyl group which may be substituted with 1 to 3 selected from a halogen, nitro, nitrile, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono or di-C_{1-4} alkyl substituted amino, C_{1-4} alkoxycarbonyl, hydroxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkylsubstituted carbamoyl, phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkyl-carbamoyl, phenyl carbamoyl and adamantan-1-yl, wherein the phenyl group can optionally have 1 to 4 substituents selected from a C_{1-4} alkyl group, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-4} alkoxycarbonyl; R^3 and n are of the same meaning as defined in claim 1 or a salt thereof to

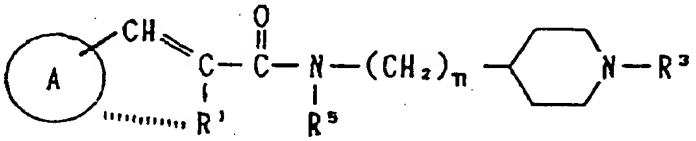
give an unsaturated carboxylic acid amide derivative represented by the formula:



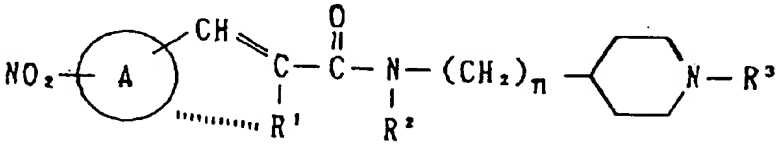
wherein each symbol is of the same meaning as defined above, or a salt thereof,
(B) subjecting a compound represented by the formula:



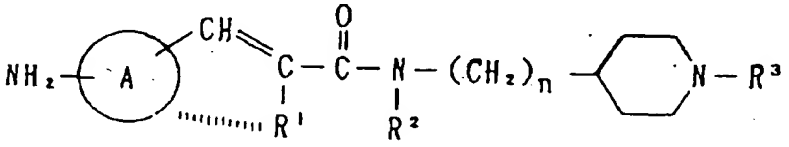
wherein each symbol is of the same meaning as defined above, to a reaction introducing a hydrocarbon residue or acylation to give an unsaturated carboxylic acid amide derivative represented by the formula:



wherein R^5 is the same as R^2 except a hydrogen atom, and the remaining symbols are of the same meaning as defined above, or a salt thereof,
(C) subjecting a compound represented by the formula:

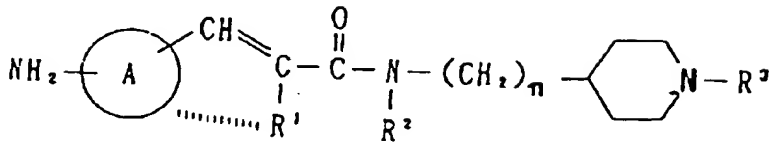


wherein R^2 is as defined in claim 1, and the remaining symbols are of the same meaning as above, or a salt thereof to reduction to give an unsaturated carboxylic acid amide derivative of the formula:

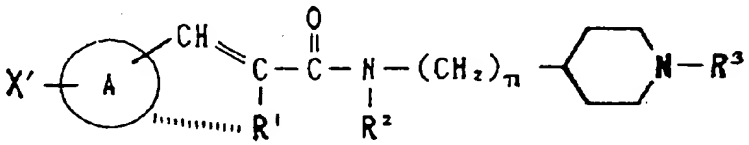


wherein each symbol is of the same meaning as above, or a salt thereof, or

(D) subjecting a compound represented by the formula:



wherein each symbol is of the same meaning as defined above, or a salt thereof to acylation to give an unsaturated carboxylic acid amide derivative represented by the formula:



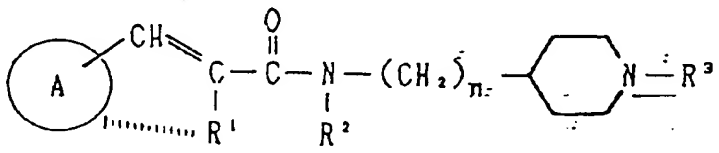
wherein X' stands for C_{1-4} alkylcarbonylamino or C_{1-4} alkylsulfonylamino group, and the remaining symbols are of the same meaning as defined above, or a salt thereof.

18. A pharmaceutical composition which contains a compound according to claim 1 together with carrier, diluent therefor.

19. Use of a compound as claimed in claim 1 as a component in the preparation of a medicament for improving cerebral functions in senile dementia.

Claims for the following Contracting State : ES

1. A process for preparing a compound of the formula:

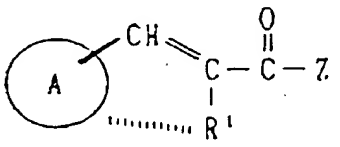


wherein ring A stands for a benzene, naphthalene, anthracene or 5- or 6-membered heterocyclic ring containing 1 to 4 hetero atoms selected from nitrogen atom, oxygen atom and sulfur atom which may be substituted with one to four substituents selected from the group consisting of a C_{1-4} alkyl, a halogen atom, nitro, cyano, hydroxy, a C_{1-4} alkoxy, a C_{1-4} alkylthio,amino, a mono- or di-C_{1-4} alkyl-substituted amino, C_{1-4} alkylcarbonylamino, C_{1-4} alkylsulfonylamino, C_{1-4} alkoxycarbonyl, hydroxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl-substituted carbamoyl, C_{1-6} alkylsulfonyl, phenyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl C_{1-4} alkylcarbamoyl, phenylcarbamoyl, phenyl C_{1-4} alkylcarbonylamino, benzoylamino, phenyl-C_{1-4} alkylsulfonyl, phenylsulfonyl, phenyl C_{1-4} alkylsulfonylamine and phenylsulfonylamino group, wherein the phenyl group or moiety may be further substituted by one or two selected from a C_{1-4} alkyl group, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-4} alkoxycarboxy groups; R^1 stands for a hydrogen atom, or a straight-chain or branched alkyl groups of 1 to 11 carbon atom, straight-chain or branched C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} monocyclic cycloalkyl, bicyclo[3,2,1]oct-2-yl, bicyclo[3,3,1]-nonan-2-yl, adamantan-1-yl, phenyl or naphthyl group which may be substituted with 1 to 3 selected from a halogen, nitro, nitrile, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono or di-C_{1-4} alkyl substituted amino, C_{1-4} alkoxycarbonyl, hydroxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-

C_{1-4} alkyl substituted carbamoyl, phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkylcarbamoyl, phenyl carbamoyl and adamantan-1-yl wherein the phenyl group can optionally have 1 to 4 substituents selected from a C_{1-4} alkyl group, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-4} alkoxycarbonyl, or together with the adjacent group -CH = C-and two carbon atoms constituting the ring A, forms 1,2-dihydronaphthalene, 6,7-dihydro-5H-benzocycloheptene, 5,6,7,8-tetra-hydrocyclooctene, 4,5-dihydrobenzo[b]thiophene, 4,5-dihydroisobenzofuran, 7,8-dihydro-quinoline or 7,8-dihydroisoquinoline which may be substituted with 1 to 3 selected from a C_{1-4} alkyl group, halogen, hydroxyl group, C_{1-4} alkyloxy group, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro, cyano and C_{1-4} alkoxycarbonyl; R^2 stands for (i) a hydrogen atom, (ii) a straight-chain or branched alkyl groups of 1 to 11 carbon atom, straight-chain or branched C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} monocyclic cycloalkyl, bicyclo[3,2,1]oct-2-yl, bicyclo[3,3,1]nonan-2-yl, adamantan-1-yl, phenyl or naphthyl group which may be substituted with 1 to 3 selected from a halogen, nitro, nitrile, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono or di-C_{1-4} alkyl substituted amino, C_{1-4} alkoxy-carbonyl, hydroxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl substituted carbamoyl, phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkylcarbamoyl, phenyl carbamoyl and adamantan-1-yl wherein the phenyl group can optionally have 1 to 4 substituents selected from a C_{1-4} alkyl group, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4}alkyl-substituted amino, nitro and C_{1-4} alkoxycarbonyl or (iii) a C_{1-6} alkylcarbonyl, C_{3-8} cycloalkylcarbonyl, C_{3-8} cycloalkyl-C_{1-6} alkylcarbonyl, C_{2-6} alkenyl or alkynylcarbonyl, benzoyl, naphthoyl, carbamoyl, mono- or di-C_{1-4} alkylcarbamoyl, mono- or di-C_{3-6} alkenyl carbamoyl, phenylcarbamoyl, naphthylcarbamoyl, diphenylcarbamoyl, sodium sulfonyl, C_{1-6} alkylsulfonyl, C_{2-6} alkenyl- or alkynyl-sulfonyl, phenylsulfonyl, naphthalenesulfonyl, C_{1-6} alkyloxycarbonyl, C_{3-8} cycloalkyloxycarbonyl, cyclopentylmethyloxycarbonyl, C_{2-7} alkenyl- or alkynyloxycarbonyl, phenyloxycarbonyl, or phenyl-C_{1-2} alkoxycarbonyl which may have further 1 to 3 substituents selected from halogen, nitro, nitrile, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono or di-C_{1-4} alkyl substituted amino, C_{1-4} alkoxycarbonyl, hydroxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl substituted carbamoyl, phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkylcarbamoyl, phenyl carbamoyl and adamantan-1-yl, wherein the phenyl group can optionally have 1 to 4 substituents selected from a C_{1-4} alkyl group, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-4} alkoxycarbonyl; R^3 stands for a straight-chain or branched alkyl groups of 1 to 11 carbon atom, straight-chain or branched C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} monocyclic cycloalkyl, bicyclo[3,2,1]oct-2-yl, bicyclo[3,3,1]nonan-2-yl, adamantan-1-yl, phenyl or naphthyl group which may be substituted with 1 to 3 selected from a halogen, nitro, nitrile, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono or di-C_{1-4} alkyl substituted amino, C_{1-4} alkoxycarbonyl, hydroxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkyl substituted carbamoyl, phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkylcarbamoyl, phenyl carbamoyl and adamantan-1-yl, wherein the phenyl group can optionally have 1 to 4 substituents selected from a C_{1-4} alkyl group, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-4} alkoxycarbonyl; and n denotes an integer ranging from 2 to 6, or salts thereof,

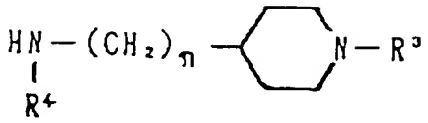
which is characterized by

(A) allowing a compound represented by a compound represented by the formula:

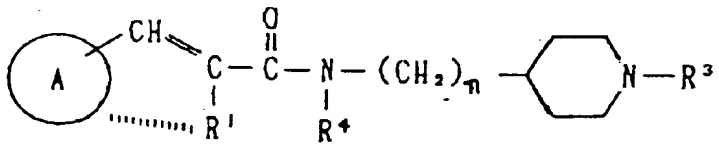


wherein Z stands for a hydroxyl group or a reactive group of carboxylic acid, and other symbols are of the same meaning as defined above,

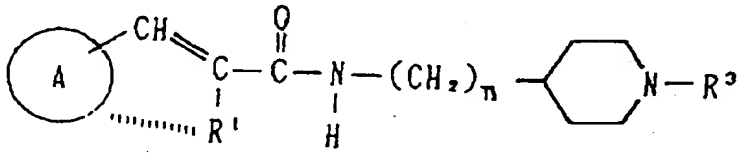
to react with a compound represented by the formula:



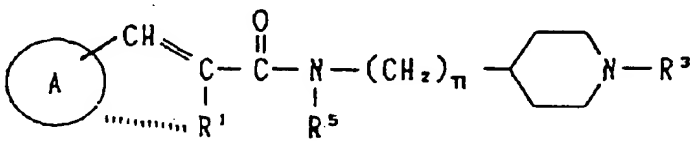
wherein R^4 stands for a hydrogen atom or a straight-chain or branched alkyl groups of 1 to 11 carbon atom, straight-chain or branched C_{2-4} alkenyl, C_{2-4} alkynyl, C_{3-7} monocyclic cycloalkyl, bicyclo[3,2,1]oct-2-yl, bicyclo[3,3,1]nonan-2-yl, adamantan-1-yl, phenyl or naphthyl group which may be substituted with 1 to 3 selected from a halogen, nitro, nitrile, hydroxy, C_{1-4} alkoxy, C_{1-4} alkylthio, amino, mono or di-C_{1-4} alkyl substituted amino, C_{1-4} alkoxycarbonyl, hydroxycarbonyl, C_{1-6} alkylcarbonyl, carbamoyl, mono- or di-C_{1-4} alkylsubstituted carbamoyl, phenyl, naphthyl, phenoxy, benzoyl, phenoxycarbonyl, phenyl-C_{1-4} alkyl-carbamoyl, phenyl carbamoyl and adamantan-1-yl, wherein the phenyl group can optionally have 1 to 4 substituents selected from a C_{1-4} alkyl group, halogen, hydroxy, benzyloxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro and C_{1-4} alkoxycarbonyl; R^3 and n are of the same meaning as defined above or a salt thereof to give an unsaturated carboxylic acid amide derivative represented by the formula:



wherein each symbol is of the same meaning as defined above, or a salt thereof,
(B) subjecting a compound represented by the formula:

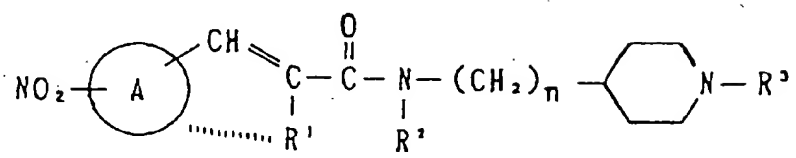


wherein each symbol is of the same meaning as defined above, to a reaction introducing a hydrocarbon residue or acylation to give an unsaturated carboxylic acid amide derivative represented by the formula:

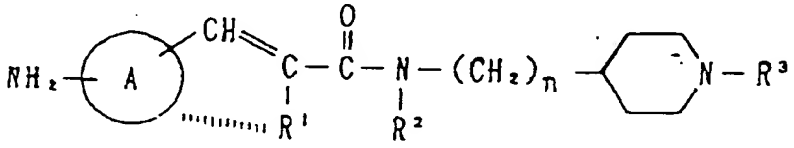


wherein R^5 is the same as R^2 except a hydrogen atom, and the remaining symbols are of the same meaning as defined above, or a salt thereof,

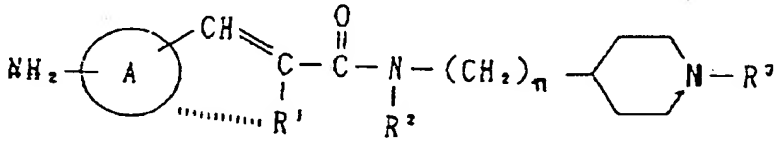
(C) subjecting a compound represented by the formula:



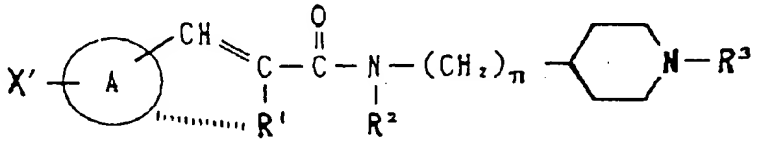
wherein R^2 is as defined above, and the remaining symbols are of the same meaning as above, or a salt thereof to reduction to give an unsaturated carboxylic acid amide derivative of the formula:



wherein each symbol is of the same meaning as above, or a salt thereof, or
(D) subjecting a compound represented by the formula:



wherein each symbol is of the same meaning as defined above, or a salt thereof to acylation to give an unsaturated carboxylic acid amide derivative represented by the formula:



wherein X' stands for C_{1-4} alkylcarbonylamino or C_{1-4} alkylsulfonylamino group, and the remaining symbols are of the same meaning as defined above, or a salt thereof.

2. Process according to claim 1, wherein the ring A is benzene.

3. Process according to claim 1, wherein the ring A is naphthalene or anthracene.

4. Process according to claim 1, wherein the ring A is a member selected from the group consisting of thiophene, furan, pyrazole, thiazole, isothiazole, oxazole, isoxazole, imidazole, triazole, tetrazole, pyridine, pyrimidine and pyridazine.

5. Process according to claim 1, wherein the ring A is unsubstituted or substituted with 1 to 3 selected from C_{1-4} alkyl, halogen, nitro, cyano, acetylamino, C_{1-4} alkoxy, benzyl, benzoylamino, C_{1-6} alkylsulfonyl, benzylsulfonyl, phenylsulfonylamino, benzylsulfonylamino, phenylcarbamoyl, methoxycarbonyl and diethoxycarbonyl.

6. Process according to claim 1, wherein R^1 is hydrogen, C_{1-11} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or C_{3-7} monocyclic cycloalkyl.

7. Process according to claim 1, wherein R^1 form a 1,2-dihydronaphthalene together with the adjacent group -CH = C- and two carbon atoms constituting the ring A.

8. Process according to claim 7, wherein the 1,2-dihydronaphthalene formed by the 5- to 7-membered ring and ring A is unsubstituted or substituted with 1 to 3 selected from C_{1-4} alkyl, halogen, C_{1-4} alkoxy, amino, mono- or di-C_{1-4} alkyl-substituted amino, nitro, cyano and C_{1-4} alkoxycarbonyl.

9. Process according to claim 1, wherein R^2 is hydrogen, C_{1-11} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or C_{3-7} monocyclic cycloalkyl.

10. Process according to claim 1, wherein n is an integer of 2, 3 or 4.

11. Process according to claim 1, wherein ring A is benzene, pyridine, furan or thiophene which may be substituted with C_{1-4} alkyl, C_{1-4} alkoxy, nitro, cyano, halogen or/and C_{1-6} alkylsulfonyl; R^1 is hydrogen, C_{1-6} alkyl or phenyl, or forms 1,2-dihydronaphthalene which may be substituted with C_{1-4} alkoxy together with the adjacent group -CH = C- and two carbon atoms of the ring A; R^2 is hydrogen, C_{1-6} alkyl or C_{1-6} alkylcarbonyl; R^3 is benzyl; and n is 2.

12. Process according to claim 1, wherein ring A is benzene, pyridine, furan or thiophene which may be substituted with C_{1-4} alkoxy; R^1 is hydrogen, C_{1-6} alkyl or phenyl, or forms 1,2-dihydronaphthalene which may be substituted with C_{1-4} alkoxy together with the adjacent group -CH = C- and two carbon atoms of the ring A; R^2 is hydrogen, C_{1-6} alkyl or C_{1-6} alkylcarbonyl; R^3 is benzyl, and n is 2.

13. Process according to claim 1, wherein ring A is benzene; R^1 is hydrogen; R^2 is hydrogen, C_{1-6} alkyl or C_{1-6} alkylcarbonyl; R^3 is benzyl; and n is 2.

14. Process according to claim 1, wherein the compound prepared is (E)-3-phenyl-N-acetyl-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-propenamide • hydrochloride.

15. Process according to claim 1, wherein the compound prepared is (E)-3-(3-pyridyl)-N-[2-(1-benzyl-piperidin-4-yl)ethyl]-2-propenamide.

16. Process according to claim 1, wherein the compound prepared is 3,4-dihydro-6,7-dimethoxy-N-[2-(1-benzylpiperidin-4-yl)-ethyl]naphthalene-2-carboxamide • hydrochloride

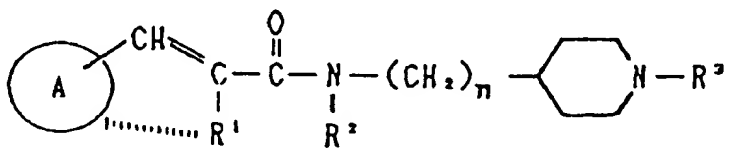
17. Process for preparing a pharmaceutical composition which comprises compounding a compound prepared according to any one of claims 1 to 16 with a conventional carrier or diluent therefor.

18. Process according to claim 17 for preparing a medicament for improving cerebral functions in senile dementia.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel



worin

Ring A für einen Benzol-, Naphthalin-, Anthracen- oder 5- bis 6-gliedrigen heterocyclischen Ring mit 1 bis 4 aus Stickstoff-Atomen, Sauerstoff-Atomen und Schwefel-Atomen ausgewählten Hetero-Atomen steht, der mit einem bis vier Substituenten substituiert sein kann, der/die ausgewählt ist/sind aus der aus einer C_{1-4}-Alkyl-Gruppe, einem Halogen-Atom, einer Nitro-Gruppe, Cyan-Gruppe, Hydroxy-Gruppe, C_{1-4}-Alkoxy-Gruppe, C_{1-4}-Alkylthio-Gruppe, Amino-Gruppe, mono- oder di-C_{1-4}-Alkyl-substituierten Amino-Gruppe, C_{1-4}-Alkylcarbonylamino-Gruppe, C_{1-4}-Alkylsulfonylamino-Gruppe, C_{1-4}-Alkoxycarbonyl-Gruppe, Hydroxycarbonyl-Gruppe, C_{1-6}-Alkylcarbonyl-Gruppe, Carbamoyl-Gruppe, mono- oder di-C_{1-4}-Alkyl-substituierten Carbamoyl-Gruppe, C_{1-6}-Alkylsulfonyl-Gruppe, Phenyl-Gruppe, Phenoxy-Gruppe, Benzoyl-Gruppe, Phenoxycarbonyl-Gruppe, Phenyl-C_{1-4}-alkylcarbamoyl-Gruppe, Phenylcarbamoyl-Gruppe, Phenyl-C_{1-4}-alkylcarbonylamino-Gruppe, Benzoylamino-Gruppe, Phenyl-C_{1-4}-alkylsulfonyl-Gruppe, Phenylsulfonyl-Gruppe, Phenyl-C_{1-4}-alkylsulfonylamin-Gruppe und Phenylsulfonylamino-Gruppe bestehenden Gruppe, worin die Phenyl-Gruppe oder -Struktureinheit weiterhin durch einen oder zwei Substituenten substituiert sein kann, die aus einer C_{1-4}-Alkyl-Gruppe, einem Halogen, einer Hydroxy-, Benzyloxy-, Amino-, mono- oder di-C_{1-4}-Alkyl-substituierten Amino, Nitro- und C_{1-4}-Alkoxycarboxy-Gruppe ausgewählt sind;

R^1 für ein Wasserstoff-Atom oder eine geradkettige oder verzweigte Alkyl-Gruppe mit 1 bis 11 Kohlenstoff-Atomen, eine geradkettige oder verzweigte C_{2-4}-Alkenyl-Gruppe, eine C_{2-4}-Alkinyl-Gruppe, eine C_{3-7}-monocyclischeCycloalkyl-Gruppe, eine Bicyclo[3,2,1]oct-2-yl-Gruppe, eine Bicyclo[3,3,1]nonan-2-yl-Gruppe, eine Adamantan-1-yl-Gruppe, eine Phenyl-Gruppe oder Naphthyl-Gruppe steht, die mit 1 bis 3 Substituenten substituiert sein kann, die aus Halogen, Nitro, Nitril, Hydroxy, C_{1-4}-Alkoxy, C_{1-4}-Alkylthio, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino-, C_{1-4}-Alkoxycarbonyl, Hydroxycarbonyl, C_{1-6}-Alkylcarbonyl, Carbamoyl, mono- oder di-C_{1-4}-Alkyl-substituiertem Carbamoyl, Phenyl, Naphthyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C_{1-4}-alkylcarbamoyl, Phenylcarbamoyl und Adamantan-1-yl ausgewählt sind, worin die Phenyl-Gruppe gegebenenfalls 1 bis 4 Substituenten haben kann, die aus einer C_{1-4}-Alkyl-Gruppe, Halogen, Hydroxy, Benzyloxy, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino, Nitro und C_{1-4}-Alkoxycarbonyl ausgewählt sind, oder
zusammen mit der benachbarten Gruppe -CH=C- und zwei den Ring A konstituierenden Kohlenstoff-Atomen 1,2-Dihydronaphthalin, 6,7-Di-hydro-5H-benzocycloheptен, 5,6,7,8-Tetrahydrocycloocten, 4,5-Dihydrobenzo[b]thiophen, 4,5-Dihydroisobenzofuran, 7,8-Dihydrochinolin oder 7,8-Dihydroisochinolin bildet, das mit 1 bis 3 Substituenten substituiert sein kann, die aus einer C_{1-4}-Alkyl-Gruppe, einem Halogen, einer Hydroxyl-Gruppe, einer C_{1-4}-Alkyloxy-Gruppe, Amino-Gruppe, mono- oder di-C_{1-4}-Alkyl-substituierten Amino-, Nitro-, Cyan- und C_{1-4}-Alkoxycarbonyl-Gruppe ausgewählt sind;

R^2 für

(i) ein Wasserstoff-Atom,

(ii) eine geradkettige oder verzweigte Alkyl-Gruppe mit 1 bis 11 Kohlenstoff-Atomen, geradkettige oder verzweigte C_{2-4}-Alkenyl-Gruppe, C_{2-4}-Alkinyl-Gruppe, C_{3-7}-monocyclische Cycloalkyl-Gruppe, eine Bicyclo[3,2,1]oct-2-yl-Gruppe, eine Bicyclo[3,3,1]-nonan-2-yl-Gruppe, eine Adamantan-1-yl-Gruppe, eine Phenyl-Gruppe oder Naphthyl-Gruppe, die mit 1 bis 3 Substituenten substituiert sein kann, die aus Halogen, Nitro, Nitril, Hydroxy, C_{1-4}-Alkoxy, C_{1-4}-Alkylthio, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino-, C_{1-4}-Alkoxycarbonyl, Hydroxycarbonyl, C_{1-6}-Alkylcarbonyl, Carbamoyl, mono- oder di-C_{1-4}-Alkyl-substituiertem Carbamoyl, Phenyl, Naphthyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C_{1-4}-alkylcarbamoyl, Phenylcarbamoyl und Adamantan-1-yl ausgewählt sind, worin die Phenyl-Gruppe gegebenenfalls 1 bis 4 Substituenten haben kann, die aus einer C_{1-4}-Alkyl-Gruppe, Halogen, Hydroxy, Benzyloxy, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino, Nitro und C_{1-4}-Alkoxycarbonyl ausgewählt sind, oder

(iii) ein C_{1-6}-Alkylcarbonyl, C_{3-8}-Cycloalkylcarbonyl, C_{3-8}-Cycloalkyl-C_{1-6}-alkylcarbonyl, C_{2-6}-Alkenyl- oder -Alkinylcarbonyl, Benzoyl, Naphthoyl, Carbamoyl, Mono- oder Di-C_{1-4}-alkylcarbamoyl, Mono- oder Di-C_{3-6}-alkenylcarbamoyl, Phenylcarbamoyl, Naphthylcarbamoyl, Diphenylcarbamoyl, Natriumsulfonyl, C_{1-6}-Alkylsulfonyl, C_{2-6}-Alkenyl- oder -Alkinylsulfonyl, Phenylsulfonyl, Naphthalinsulfonyl, C_{1-6}-Alkyloxycarbonyl,

C_{3-8}-Cycloalkyloxycarbonyl, Cyclopentylmethyloxycarbonyl, C_{2-7}-Alkenyl- oder -Alkinyloxycarbonyl, Phenyloxycarbonyl oder Phenyl-C_{1-2}-alkoxycarbonyl steht, das weiterhin 1 bis 3 Substituenten haben kann, die ausgewählt sind aus Halogen, Nitro, Nitril, Hydroxy, C_{1-4}-Alkoxy, C_{1-4}-Alkylthio, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino-, C_{1-4}-Alkoxycarbonyl, Hydroxycarbonyl, C_{1-5}-Alkylcarbonyl, Carbamoyl, mono- oder di-C_{1-4}-Alkyl-substituiertem Carbamoyl, Phenyl, Naphthyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C_{1-4}-alkylcarbamoyl, Phenylcarbamoyl und Adamantan-1-yl, worin die Phenyl-Gruppe gegebenenfalls 1 bis 4 Substituenten haben kann, die aus einer C_{1-4}-Alkyl-Gruppe, Halogen, Hydroxy, Benzyloxy, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino, Nitro und C_{1-4}-Alkoxycarbonyl ausgewählt sind;

R^3 für eine geradkettige oder verzweigte Alkyl-Gruppe mit 1 bis 11 Kohlenstoff-Atomen, geradkettige oder verzweigte C_{2-4}-Alkenyl-Gruppe, C_{2-4}-Alkinyl-Gruppe, C_{3-7}-monocyclische Cycloalkyl-Gruppe, eine Bicyclo-[3,2,1]oct-2-yl-Gruppe, eine Bicyclo[3,3,1]nonan-2-yl-Gruppe, eine Adamantan-1-yl-Gruppe, eine Phenyl-Gruppe oder Naphthyl-Gruppe steht, die mit 1 bis 3 Substituenten substituiert sein kann, die aus Halogen, Nitro, Nitril, Hydroxy, C_{1-4}-Alkoxy, C_{1-4}-Alkylthio, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino-, C_{1-4}-Alkoxycarbonyl, Hydroxycarbonyl, C_{1-5}-Alkylcarbonyl, Carbamoyl, mono- oder di-C_{1-4}-Alkyl-substituiertem Carbamoyl, Phenyl, Naphthyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C_{1-4}-alkylcarbamoyl, Phenylcarbamoyl und Adamantan-1-yl ausgewählt sind, worin die Phenyl-Gruppe gegebenenfalls 1 bis 4 Substituenten haben kann, die aus einer C_{1-4}-Alkyl-Gruppe, Halogen, Hydroxy, Benzyloxy, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino, Nitro und C_{1-4}-Alkoxycarbonyl ausgewählt sind, und

n eine ganze Zahl im Bereich von 2 bis 6 bezeichnet,

oder deren Salze.

2. Verbindung nach Anspruch 1, worin der Ring A Benzol ist.

3. Verbindung nach Anspruch 1, worin der Ring A Naphthalin oder Anthracen ist.

4. Verbindung nach Anspruch 1, worin der Ring A eine Struktureinheit ist, die aus der aus Thiophen, Furan, Pyrazol, Thiazol, Isothiazol, Oxazol, Isoxazol, Imidazol, Triazol, Tetrazol, Pyridin, Pyrimidin und Pyridazin bestehenden Gruppe ausgewählt ist.

5. Verbindung nach Anspruch 1, worin der Ring A unsubstituiert oder mit einem bis 3 Substituenten substituiert ist, die aus C_{1-4}-Alkyl, Halogen, Nitro, Cyan, Acetylamino, C_{1-4}-Alkoxy, Benzyl, Benzoylamino, C_{1-6}-Alkylsulfonyl, Benzylsulfonyl, Phenylsulfonylamino, Benzylsulfonylamino, Phenylcarbamoyl, Methoxycarbonyl und Diethoxycarbonyl ausgewählt sind.

6. Verbindung nach Anspruch 1, worin R^1 Wasserstoff, C_{1-11}-Alkyl, C_{2-4}-Alkenyl, C_{2-4}-Alkinyl oder monocyclisches C_{3-7}-Cycloalkyl ist.

7. Verbindung nach Anspruch 1, worin R^1 zusammen mit der benachbarten Gruppe -CH=C- und zwei den Ring konstituierenden Kohlenstoff-Atomen ein 1,2-Dihydronaphthalin bildet.

8. Verbindung nach Anspruch 7, worin das durch den 5- bis 7-gliedrigen Ring und den Ring A gebildete 1,2-Dihydronaphthalin unsubstituiert oder durch 1 bis 3 Substituenten substituiert ist, die aus C_{1-4}-Alkyl, Halogen, C_{1-4}-Alkoxy, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino, Nitro, Cyan und C_{1-4}-Alkoxycarbonyl ausgewählt sind.

9. Verbindung nach Anspruch 1, worin R^2 Wasserstoff, C_{1-11}-Alkyl, C_{2-4}-Alkenyl, C_{2-4}-Alkinyl oder monocyclisches C_{3-7}-Cycloalkyl ist.

10. Verbindung nach Anspruch 1, worin n eine ganze Zahl von 2, 3 oder 4 ist.

11. Verbindung nach Anspruch 1, worin

Ring A Benzol, Pyridin, Furan oder Thiophen ist, das mit C_{1-4}-Alkyl, C_{1-4}-Alkoxy, Nitro, Cyan, Halogen oder/und C_{1-6}-Alkylsulfonyl substituiert sein kann;

R^1 Wasserstoff, C_{1-6}-Alkyl oder Phenyl ist oder zusammen mit der benachbarten Gruppe

-CH = C- und zwei den Ring A konstituierenden Kohlenstoff-Atomen ein 1,2-Dihydronaphthalin bildet, das durch C_{1-4}-Alkoxy substituiert sein kann;
R^2 Wasserstoff, C_{1-6}-Alkyl oder C_{1-6}-Alkylcarbonyl ist;
R^3 Benzyl ist; und
n 2 ist.

12. Verbindung nach Anspruch 1, worin
Ring A Benzol, Pyridin, Furan oder Thiophen ist, das mit C_{1-4}-Alkoxy substituiert sein kann;
R^1 Wasserstoff, C_{1-6}-Alkyl oder Phenyl ist oder zusammen mit der benachbarten Gruppe -CH = C- und zwei den Ring A konstituierenden Kohlenstoff-Atomen ein 1,2-Dihydronaphthalin bildet, das durch C_{1-4}-Alkoxy substituiert sein kann;
R^2 Wasserstoff, C_{1-6}-Alkyl oder C_{1-6}-Alkylcarbonyl ist;
R^3 Benzyl ist; und
n 2 ist.

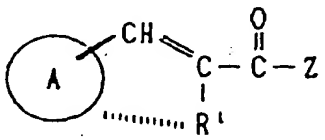
13. Verbindung nach Anspruch 1, worin
Ring A Benzol ist;
R^1 Wasserstoff ist;
R^2 Wasserstoff, C_{1-6}-Alkyl oder C_{1-6}-Alkylcarbonyl ist;
R^3 Benzyl ist; und
n 2 ist.

14. Verbindung nach Anspruch 1, die (E)-3-Phenyl-N-acetyl-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-propenamid • hydrochlorid ist.

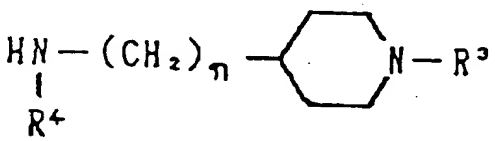
15. Verbindung nach Anspruch 1, die (E)-3-(3-Pyridyl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-propenamid ist.

16. Verbindung nach Anspruch 1, die 3,4-Dihydro-6,7-dimethoxy-N-[2-(1-benzylpiperidin-4-yl)-ethyl]-naphthalin-2-carboxamid • hydrochlorid ist.

17. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß
(A) man eine Verbindung der Formel



worin
Z für eine Hydroxyl-Gruppe oder eine reaktions-fähige Gruppe einer Carbonsäure steht und die anderen Symbole die in Anspruch 1 angegebenen Bedeutungen haben,
mit einer Verbindung der Formel

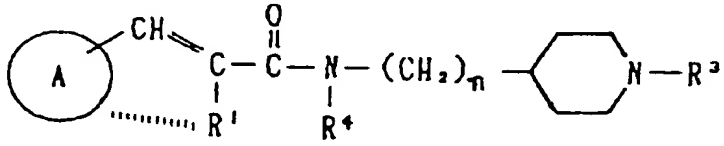


worin

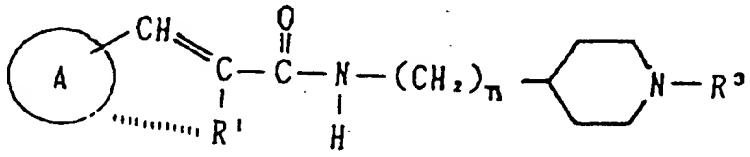
R^4 für ein Wasserstoff-Atom oder eine geradkettige oder verzweigte Alkyl-Gruppe mit 1 bis 11 Kohlenstoff-Atomen, geradkettige oder verzweigte C_{2-4}-Alkenyl-Gruppe, C_{2-4}-Alkinyl-Gruppe, C_{3-7}-monocyclische Cycloalkyl-Gruppe, eine Bicyclo-[3,2,1]oct-2-yl-Gruppe, eine Bicyclo[3,3,1]nonan-2-yl-Gruppe, eine Adamantan-1-yl-Gruppe, eine Phenyl-Gruppe oder Naphthyl-Gruppe steht, die mit 1 bis 3 Substituenten substituiert sein kann, die aus Halogen, Nitro, Nitril, Hydroxy, C_{1-4}-Alkoxy, C_{1-4}-Alkylthio, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino-, C_{1-4}-Alkoxycarbonyl, Hydroxycarbonyl, C_{1-5}-Alkylcarbonyl, Carbamoyl, mono- oder di-C_{1-4}-Alkyl-substituiertem Carbamoyl, Phenyl, Naphthyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C_{1-4}-alkylcarbamoyl, Phenylcarbamoyl und Adamantan-1-yl ausgewählt sind, worin die Phenyl-Gruppe gegebenenfalls 1 bis 4 Substituenten haben kann, die aus einer C_{1-4}-Alkyl-Gruppe, Halogen, Hydroxy, Benzyloxy, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino, Nitro und C_{1-4}-Alkoxycarbonyl ausgewählt sind,

R^3 und n die in Anspruch 1 angegebenen Bedeutungen haben,

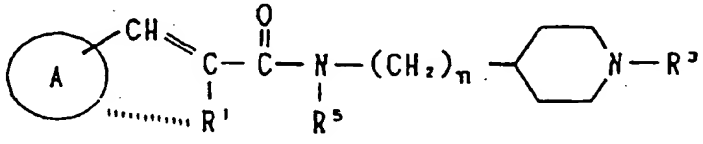
oder einem Salz derselben reagieren läßt, um ein ungesättigtes Carbonsäureamid-Derivat der Formel



worin
jedes der Symbole die oben angegebenen Bedeutungen hat,
oder ein Salz desselben zu erhalten,
(B) eine Verbindung der Formel



worin
jedes der Symbole die oben angegebenen Bedeutungen hat,
einer Reaktion zur Einführung eines Kohlenwasserstoff-Restes oder Acylierung unterworfen wird, um ein ungesättigtes Carbonsäureamid-Derivat der Formel

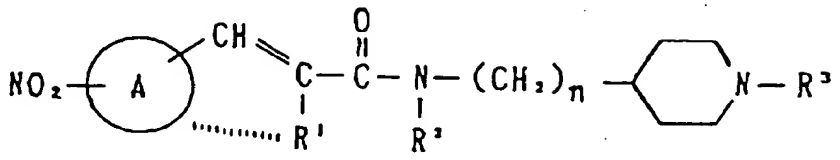


worin

R^5 gleich R^2, mit Ausnahme eines Wasserstoff-Atoms, ist und die übrigen Symbole die oben angegebenen Bedeutungen haben,

oder ein Salz desselben zu erhalten,

(C) eine Verbindung der Formel

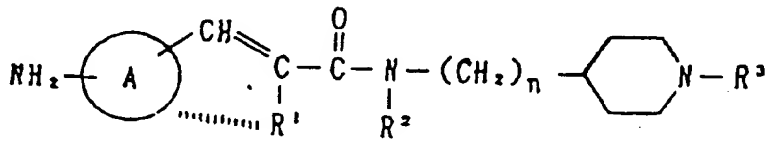


worin

R^2 die in Anspruch 1 angegebenen Bedeutungen hat und

die übrigen Symbole die oben angegebenen Bedeutungen haben,

einer Reduktion unterworfen wird, um ein ungesättigtes Carbonsäureamid-Derivat der Formel

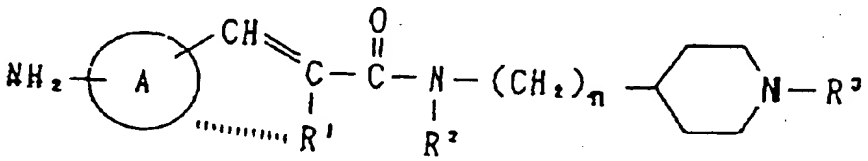


worin

jedes der Symbole die oben angegebenen Bedeutungen hat,

oder ein Salz desselben zu erhalten, oder

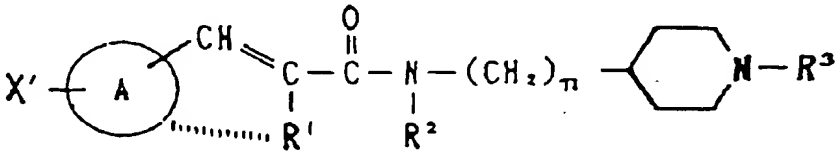
(D) eine Verbindung der Formel



worin

jedes der Symbole die oben angegebenen Bedeutungen hat, oder ein Salz derselben

einer Acylierung unterworfen wird, um ein ungesättigtes Carbonsäureamid-Derivat der Formel



worin

X' für eine C_{1-4}-Alkylcarbonylamino- oder C_{1-4}-Alkylsulfonylamino-Gruppe steht und

die übrigen Symbole die oben angegebenen Bedeutungen haben,

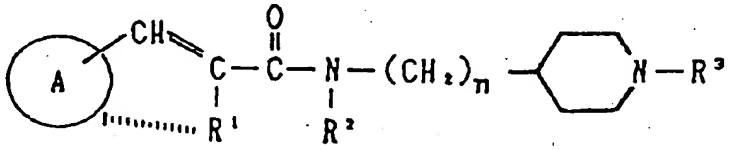
oder ein Salz desselben zu erhalten.

18. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung nach Anspruch 1 zusammen mit einem Träger oder Verdünnungsmittel für diese.

19. Verwendung einer Verbindung nach Anspruch 1 als Komponente bei der Herstellung eines Medikaments zur Verbesserung der Hirnfunktionen bei seniler Demenz.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer Verbindung der Formel



worin

Ring A für einen Benzol-, Naphthalin-, Anthracen- oder 5- bis 6-gliedrigen heterocyclischen Ring mit 1 bis 4 aus Stickstoff-Atomen, Sauerstoff-Atomen und Schwefel-Atomen ausgewählten Hetero-Atomen steht, der mit einem bis vier Substituenten substituiert sein kann, der/die ausgewählt ist/sind aus der aus einer C_{1-4}-Alkyl-Gruppe, einem Halogen-Atom, einer Nitro-Gruppe, Cyan-Gruppe, Hydroxy-Gruppe, C_{1-4}-Alkoxy-Gruppe, C_{1-4}-Alkylthio-Gruppe, Amino-Gruppe, mono- oder di-C_{1-4}-Alkyl-substituierten Amino-Gruppe, C_{1-4}-Alkylcarbonylamino-Gruppe, C_{1-4}-Alkylsulfonylamino-Gruppe, C_{1-4}-Alkoxycarbonyl-Gruppe, Hydroxycarbonyl-Gruppe, C_{1-6}-Alkylcarbonyl-Gruppe, Carbamoyl-Gruppe, mono- oder di-C_{1-4}-Alkyl-substituierten Carbamoyl-Gruppe, C_{1-6}-Alkylsulfonyl-Gruppe, Phenyl-Gruppe, Phenoxy-Gruppe, Benzoyl-Gruppe, Phenoxycarbonyl-Gruppe, Phenyl-C_{1-4}-alkylcarbamoyl-Gruppe, Phenylcarbamoyl-Gruppe, Phenyl-C_{1-4}-alkylcarbonylamino-Gruppe, Benzoylamino-Gruppe, Phenyl-C_{1-4}-alkylsulfonyl-Gruppe, Phenylsulfonyl-Gruppe, Phenyl-C_{1-4}-alkylsulfonylamin-Gruppe und Phenylsulfonylamino-Gruppe bestehenden Gruppe, worin die Phenyl-Gruppe oder -Struktureinheit weiterhin durch einen oder zwei Substituenten substituiert sein kann, die aus einer C_{1-4}-Alkyl-Gruppe, einem Halogen, einer Hydroxy-, Benzyloxy-, Amino-, mono- oder di-C_{1-4}-Alkyl-substituierten Amino-, Nitro- und C_{1-4}-Alkoxycarboxy-Gruppe ausgewählt sind;

R^1 für ein Wasserstoff-Atom oder eine geradkettige oder verzweigte Alkyl-Gruppe mit 1 bis 11 Kohlenstoff-Atomen, eine geradkettige oder verzweigte C_{2-4}-Alkenyl-Gruppe, eine C_{2-4}-Alkinyl-Gruppe, eine C_{3-7}-monocyclischeCycloalkyl-Gruppe, eine Bicyclo[3,2,1]oct-2-yl-Gruppe, eine Bicyclo[3,3,1]nonan-2-yl-Gruppe, eine Adamantan-1-yl-Gruppe, eine Phenyl-Gruppe oder Naphthyl-Gruppe steht, die mit 1 bis 3 Substituenten substituiert sein kann, die aus Halogen, Nitro, Nitril, Hydroxy, C_{1-4}-Alkoxy, C_{1-4}-Alkylthio, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino-, C_{1-4}-Alkoxycarbonyl, Hydroxycarbonyl, C_{1-6}-Alkylcarbonyl, Carbamoyl, mono- oder di-C_{1-4}-Alkyl-substituiertem Carbamoyl, Phenyl, Naphthyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C_{1-4}-alkylcarbamoyl, Phenylcarbamoyl und Adamantan-1-yl ausgewählt sind, worin die Phenyl-Gruppe gegebenenfalls 1 bis 4 Substituenten haben kann, die aus einer C_{1-4}-Alkyl-Gruppe, Halogen, Hydroxy, Benzyloxy, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino, Nitro und C_{1-4}-Alkoxycarbonyl ausgewählt sind, oder
zusammen mit der benachbarten Gruppe -CH = C- und zwei den Ring A konstituierenden Kohlenstoff-Atomen 1,2-Dihydronaphthalin, 6,7-Di-hydro-5H-benzocyclohepten, 5,6,7,8-Tetrahydrocycloocten, 4,5-Dihydrobenzo[b]thiophen, 4,5-Dihydroisobenzofuran, 7,8-Dihydrochinolin oder 7,8-Dihydroisochinolin bildet, das mit 1 bis 3 Substituenten substituiert sein kann, die aus einer C_{1-4}-Alkyl-Gruppe, einem Halogen, einer Hydroxyl-Gruppe, einer C_{1-4}-Alkyloxy-Gruppe, Amino-Gruppe, mono- oder di-C_{1-4}-Alkyl-substituierten Amino-, Nitro-, Cyan- und C_{1-4}-Alkoxycarbonyl-Gruppe ausgewählt sind;

R^2 für

(i) ein Wasserstoff-Atom,
(ii) eine geradkettige oder verzweigte Alkyl-Gruppe mit 1 bis 11 Kohlenstoff-Atomen, geradkettige oder verzweigte C_{2-4}-Alkenyl-Gruppe, C_{2-4}-Alkinyl-Gruppe, C_{3-7}-monocyclische Cycloalkyl-Gruppe, eine Bicyclo[3,2,1]oct-2-yl-Gruppe, eine Bicyclo[3,3,1]-nonan-2-yl-Gruppe, eine Adamantan-1-yl-Gruppe, eine Phenyl-Gruppe oder Naphthyl-Gruppe, die mit 1 bis 3 Substituenten substituiert sein kann, die aus Halogen, Nitro, Nitril, Hydroxy, C_{1-4}-Alkoxy, C_{1-4}-Alkylthio, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino-, C_{1-4}-Alkoxycarbonyl, Hydroxycarbonyl, C_{1-6}-Alkylcarbonyl, Carbamoyl, mono- oder di-C_{1-4}-Alkyl-substituiertem Carbamoyl, Phenyl, Naphthyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C_{1-4}-alkylcarbamoyl, Phenylcarbamoyl und Adamantan-1-yl ausgewählt sind, worin die Phenyl-Gruppe gegebenenfalls 1 bis 4 Substituenten haben kann, die aus einer C_{1-4}-Alkyl-Gruppe, Halogen, Hydroxy, Benzyloxy, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino, Nitro und C_{1-4}-Alkoxycarbonyl ausgewählt sind, oder
(iii) ein C_{1-6}-Alkylcarbonyl, C_{3-8}-Cycloalkylcarbonyl, C_{3-8}-Cycloalkyl-C_{1-6}-alkylcarbonyl, C_{2-6}-Alkenyl- oder -Alkinylcarbonyl, Benzoyl, Naphthoyl, Carbamoyl, Mono- oder Di-C_{1-4}-alkylcarbamoyl, Mono- oder Di-C_{3-6}-alkenylcarbamoyl, Phenylcarbamoyl, Naphthylcarbamoyl, Diphenylcarbamoyl, Natriumsulfonyl, C_{1-6}-Alkylsulfonyl, C_{2-6}-Alkenyl- oder -Alkinylsulfonyl, Phenylsulfonyl, Naphthalinsulfonyl, C_{1-6}-Alkyloxycarbonyl, C_{3-8}-Cycloalkyloxycarbonyl, Cyclopentylmethyloxycarbonyl, C_{2-7}-Alkenyl- oder -Alkinyloxycarbonyl, Phenyloxycarbonyl oder Phenyl-C_{1-2}-alkoxycarbonyl steht, das weiterhin 1 bis 3 Substituenten haben kann, die ausgewählt sind aus Halogen, Nitro, Nitril, Hydroxy, C_{1-4}-Alkoxy, C_{1-4}-Alkylthio, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino-, C_{1-4}-Alkoxycarbonyl, Hydroxycarbonyl, C_{1-6}-Alkylcarbonyl, Carbamoyl, mono- oder di-C_{1-4}-Alkyl-substituiertem Carbamoyl, Phenyl, Naphthyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C_{1-4}-alkylcarbamoyl, Phenylcarbamoyl und Adamantan-1-yl, worin die Phenyl-Gruppe gegebenenfalls 1 bis 4 Substituenten haben kann, die aus einer C_{1-4}-Alkyl-Gruppe, Halogen, Hydroxy, Benzyloxy, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino, Nitro und C_{1-4}-Alkoxycarbonyl ausgewählt sind;

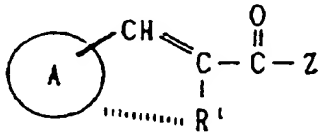
R^3 für eine geradkettige oder verzweigte Alkyl-Gruppe mit 1 bis 11 Kohlenstoff-Atomen, geradkettige oder verzweigte C_{2-4}-Alkenyl-Gruppe, C_{2-4}-Alkinyl-Gruppe, C_{3-7}-monocyclische Cycloalkyl-Gruppe, eine Bicyclo-[3,2,1]oct-2-yl-Gruppe, eine Bicyclo[3,3,1]nonan-2-yl-Gruppe, eine Adamantan-1-yl-Gruppe, eine Phenyl-Gruppe oder Naphthyl-Gruppe steht, die mit 1 bis 3 Substituenten substituiert sein kann, die aus Halogen, Nitro, Nitril, Hydroxy, C_{1-4}-Alkoxy, C_{1-4}-Alkylthio, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino-, C_{1-4}-Alkoxycarbonyl, Hydroxycarbonyl, C_{1-6}-Alkylcarbonyl, Carbamoyl, mono- oder di-C_{1-4}-Alkyl-substituiertem Carbamoyl, Phenyl, Naphthyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C_{1-4}-alkylcarbamoyl, Phenylcarbamoyl und Adamantan-1-yl ausgewählt sind, worin die Phenyl-Gruppe gegebenenfalls 1 bis 4 Substituenten haben kann, die aus einer C_{1-4}-Alkyl-Gruppe, Halogen, Hydroxy, Benzyloxy, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino, Nitro und C_{1-4}-Alkoxycarbonyl ausgewählt sind, und

n eine ganze Zahl im Bereich von 2 bis 6 bezeichnet,

oder von Salzen derselben,

dadurch gekennzeichnet, daß

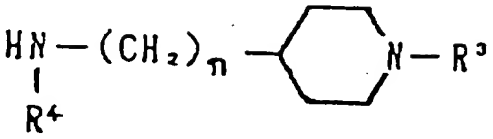
(A) man eine Verbindung der Formel



worin

Z für eine Hydroxyl-Gruppe oder eine reaktions-fähige Gruppe einer Carbonsäure steht und die anderen Symbole die oben angegebenen Bedeutungen haben,

mit einer Verbindung der Formel

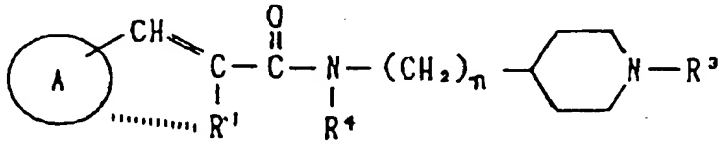


worin

R^4 für ein Wasserstoff-Atom oder eine geradkettige oder verzweigte Alkyl-Gruppe mit 1 bis 11 Kohlenstoff-Atomen, geradkettige oder verzweigte C_{2-4}-Alkenyl-Gruppe, C_{2-4}-Alkinyl-Gruppe, C_{3-7}-monocyclische Cycloalkyl-Gruppe, eine Bicyclo-[3,2,1]oct-2-yl-Gruppe, eine Bicyclo[3,3,1]nonan-2-yl-Gruppe, eine Adamantan-1-yl-Gruppe, eine Phenyl-Gruppe oder Naphthyl-Gruppe steht, die mit 1 bis 3 Substituenten substituiert sein kann, die aus Halogen, Nitro, Nitril, Hydroxy, C_{1-4}-Alkoxy, C_{1-4}-Alkylthio, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino-, C_{1-4}-Alkoxycarbonyl, Hydroxycarbonyl, C_{1-5}-Alkylcarbonyl, Carbamoyl, mono- oder di-C_{1-4}-Alkyl-substituiertem Carbamoyl, Phenyl, Naphthyl, Phenoxy, Benzoyl, Phenoxycarbonyl, Phenyl-C_{1-4}-alkylcarbamoyl, Phenylcarbamoyl und Adamantan-1-yl ausgewählt sind, worin die Phenyl-Gruppe gegebenenfalls 1 bis 4 Substituenten haben kann, die aus einer C_{1-4}-Alkyl-Gruppe, Halogen, Hydroxy, Benzyloxy, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino, Nitro und C_{1-4}-Alkoxycarbonyl ausgewählt sind,

R^3 und n die oben angegebenen Bedeutungen haben,

oder einem Salz derselben reagieren läßt, um ein ungesättigtes Carbonsäureamid-Derivat der Formel

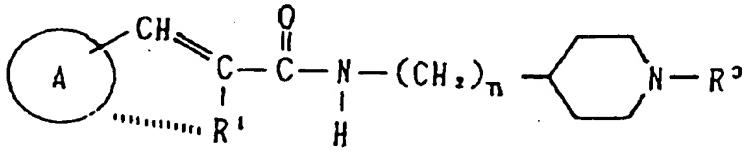


worin

jedes der Symbole die oben angegebenen Bedeutungen hat,

oder ein Salz desselben zu erhalten,

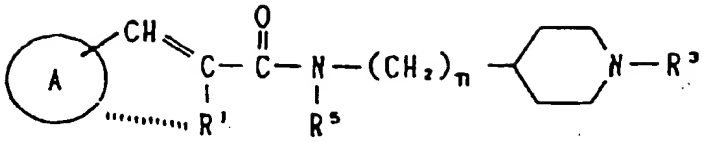
(B) eine Verbindung der Formel



worin

jedes der Symbole die oben angegebenen Bedeutungen hat,

einer Reaktion zur Einführung eines Kohlenwasserstoff-Restes oder Acylierung unterworfen wird, um ein ungesättigtes Carbonsäureamid-Derivat der Formel

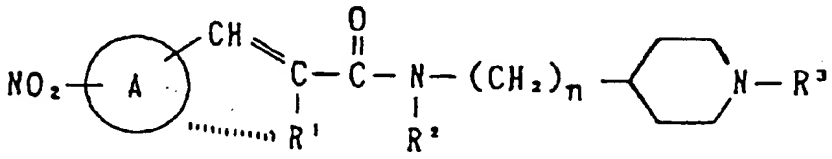


worin

R^5 gleich R^2, mit Ausnahme eines Wasserstoff-Atoms, ist und die übrigen Symbole die oben angegebenen Bedeutungen haben,

oder ein Salz desselben zu erhalten,

(C) eine Verbindung der Formel

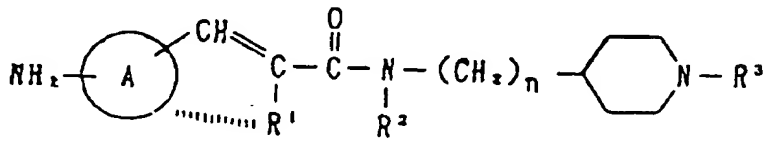


worin

R^2 die oben angegebenen Bedeutungen hat und

die übrigen Symbole die oben angegebenen Bedeutungen haben,

einer Reduktion unterworfen wird, um ein ungesättigtes Carbonsäureamid-Derivat der Formel

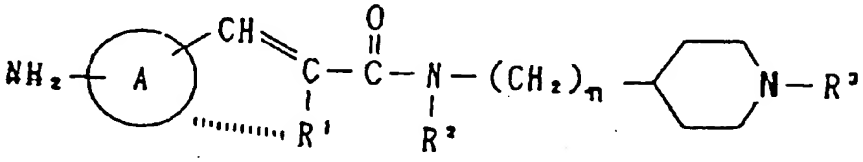


worin

jedes der Symbole die oben angegebenen Bedeutungen hat,

oder ein Salz desselben zu erhalten, oder

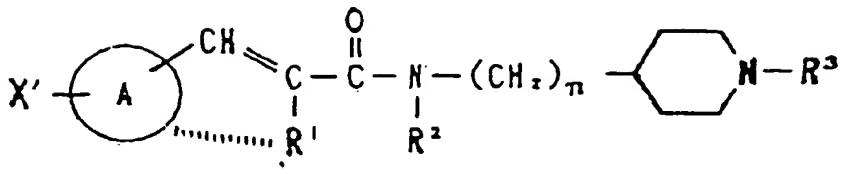
(D) eine Verbindung der Formel



worin

jedes der Symbole die oben angegebenen Bedeutungen hat, oder ein Salz derselben

einer Acylierung unterworfen wird, um ein ungesättigtes Carbonsäureamid-Derivat der Formel



worin

X' für eine C_{1-4}-Alkylcarbonylamino- oder C_{1-4}-Alkylsulfonylamino-Gruppe steht und die übrigen Symbole die oben angegebenen Bedeutungen haben,
oder ein Salz desselben zu erhalten.

2. Verfahren nach Anspruch 1, worin der Ring A Benzol ist.

3. Verfahren nach Anspruch 1, worin der Ring A Naphthalin oder Anthracen ist.

4. Verfahren nach Anspruch 1, worin der Ring A eine Struktureinheit ist, die aus der aus Thiophen, Furan, Pyrazol, Thiazol, Isothiazol, Oxazol, Isoxazol, Imidazol, Triazol, Tetrazol, Pyridin, Pyrimidin und Pyridazin bestehenden Gruppe ausgewählt ist.

5. Verfahren nach Anspruch 1, worin der Ring A unsubstituiert oder mit einem bis 3 Substituenten substituiert ist, die aus C_{1-4}-Alkyl, Halogen, Nitro, Cyan, Acetylamino, C_{1-4}-Alkoxy, Benzyl, Benzoylamino, C_{1-6}-Alkylsulfonyl, Benzylsulfonyl, Phenylsulfonylamino, Benzylsulfonylamino, Phenylcarbamoyl, Methoxycarbonyl und Diethoxycarbonyl ausgewählt sind.

6. Verfahren nach Anspruch 1, worin R^1 Wasserstoff, C_{1-11}-Alkyl, C_{2-4}-Alkenyl, C_{2-4}-Alkinyl oder monocyclisches C_{3-7}-Cycloalkyl ist.

7. Verfahren nach Anspruch 1, worin R^1 zusammen mit der benachbarten Gruppe -CH = C- und zwei den Ring A konstituierenden Kohlenstoff-Atomen ein 1,2-Dihydronaphthalin bildet.

8. Verfahren nach Anspruch 7, worin das durch den 5- bis 7-gliedrigen Ring und den Ring A gebildete 1,2-Dihydronaphthalin unsubstituiert oder durch 1 bis 3 Substituenten substituiert ist, die aus C_{1-4}-Alkyl, Halogen, C_{1-4}-Alkoxy, Amino, mono- oder di-C_{1-4}-Alkyl-substituiertem Amino, Nitro, Cyan und C_{1-4}-Alkoxycarbonyl ausgewählt sind.

9. Verfahren nach Anspruch 1, worin R^2 Wasserstoff, C_{1-11}-Alkyl, C_{2-4}-Alkenyl, C_{2-4}-Alkinyl oder monocyclisches C_{3-7}-Cycloalkyl ist.

10. Verfahren nach Anspruch 1, worin n eine ganze Zahl von 2, 3 oder 4 ist.

11. Verfahren nach Anspruch 1, worin

Ring A	Benzol, Pyridin, Furan oder Thiophen ist, das mit C_{1-4}-Alkyl, C_{1-4}-Alkoxy, Nitro, Cyan, Halogen oder/und C_{1-6}-Alkylsulfonyl substituiert sein kann;
R^1	Wasserstoff, C_{1-6}-Alkyl oder Phenyl ist oder zusammen mit der benachbarten Gruppe -CH = C- und zwei den Ring A konstituierenden Kohlenstoff-Atomen ein 1,2-Dihydronaphthalin bildet, das durch C_{1-4}-Alkoxy substituiert sein kann;
R^2	Wasserstoff, C_{1-6}-Alkyl oder C_{1-6}-Alkylcarbonyl ist;
R^3	Benzyl ist; und
n	2 ist.

12. Verfahren nach Anspruch 1, worin

Ring A	Benzol, Pyridin, Furan oder Thiophen ist, das mit C_{1-4}-Alkoxy substituiert sein kann;
R^1	Wasserstoff, C_{1-6}-Alkyl oder Phenyl ist oder zusammen mit der benachbarten Gruppe -CH = C- und zwei den Ring A konstituierenden Kohlenstoff-Atomen ein 1,2-Dihydronaphthalin bildet, das durch C_{1-4}-Alkoxy substituiert sein kann;

R^2 Wasserstoff, C_{1-6}-Alkyl oder C_{1-6}-Alkylcarbonyl ist;
R^3 Benzyl ist; und
n 2 ist.

13. Verfahren nach Anspruch 1, worin
Ring A Benzol ist;
R^1 Wasserstoff ist;
R^2 Wasserstoff, C_{1-6}-Alkyl oder C_{1-6}-Alkylcarbonyl ist;
R^3 Benzyl ist; und
n 2 ist.

14. Verfahren nach Anspruch 1, worin die hergestellt Verbindung (E)-3-Phenyl-N-acetyl-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-propenamid•hydrochlorid ist.

15. Verfahren nach Anspruch 1, worin die hergestellte Verbindung (E)-3-(3-Pyridyl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-propenamid ist.

16. Verfahren nach Anspruch 1, worin die hergestellte Verbindung 3,4-Dihydro-6,7-dimethoxy-N-[2-(1-benzylpiperidin-4-yl)-ethyl]naphthalin-2-carboxamid•hydrochlorid ist.

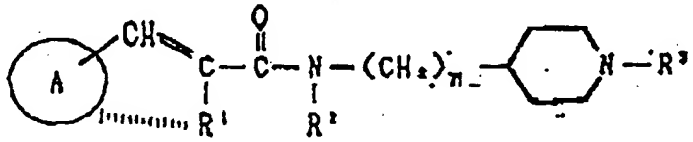
17. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, umfassend das Kompoundieren einer nach irgendeinem der Ansprüche 1 bis 16 hergestellten Verbindung mit einem konventionellen Träger oder Verdünnungsmittel für diese.

18. Verfahren nach Anspruch 17 zur Herstellung eines Medikaments zur Verbesserung der Hirnfunktionen bei seniler Demenz.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Composé de formule



dans laquelle le cycle A représente un groupe benzène, naphtalène, anthracène ou un cycle hétérocyclique à 5 ou 6 chaînons comportant de 1 à 4 hétéroatomes choisis parmi l'azote, l'oxygène et le soufre, le cycle pouvant être substitué par 1 à 4 substituants choisis dans le groupe constitué des substituants alkyle en C_1-C_4, halogène, nitro, cyano, hydroxy, alcoxy en C_1-C_4, alkylthio en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, (alkyle en C_1-C_4)-carbonylamino, (alkyle en C_1-C_4)-sulfonylamino, (alkoxy en C_1-C_4)-carbonyle, hydroxycarbonyle, (alkyle en C_1-C_6)-carbonyle, carbamoyle, mono- ou di-(alkyle en C_1-C_4)-carbamoyle, (alkyle en C_1-C_6)-sulfonyle, phényle, phénoxy, benzoyle, phénoxycarbonyle, phényl-(alkyle en C_1-C_4)-carbamoyle, phénylcarbamoyle, phényl-(alkyle en C_1-C_4)-carbonylamino, benzoylamino, phényl-(alkyle en C_1-C_4)-sulfonyle, phénylsulfonyle, phényl-(alkyle en C_1-C_4)-sulfonylamino et phénylsulfonylamino, dans lesquels le groupe ou le motif phényle peut être à son tour substitué par un ou deux résidus choisis parmi les groupes alkyle en C_1-C_4, halogéno, hydroxy, benzyloxy, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro et (alcoxy en C_1-C_4)-carboxy, R^1 représente un atome d'hydrogène ou un groupe alkyle à chaîne linéaire ou ramifiée comportant de 1 à 11 atomes de carbone, alcényle en C_2-C_4 à chaîne ramifiée ou linéaire, alcynyle en C_2-C_4 cycloalkyle en C_3-C_7 monocyclique, bicyclo[3,2,1]oct-2-yle, bicyclo[3,3,1]nonan-2-yle, adamantan-1-yle, phényle ou naphtyle pouvant être substitué par 1 à 3 substituants choisis parmi les halogéno, nitro, nitrile, hydroxy, alcoxy en C_1-C_4, alkylthio en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, (alcoxy en C_1-C_4)-carbonyle, hydroxycarbonyle, (alkyle en C_1-C_6)-carbonyle, carbamoyle, mono- ou di-(alkyle en C_1-C_4)-carbamoyle, phényle, naphtyle, phénoxy, benzoyle, phénoxycarbonyle, phényl-(alkyle en C_1-C_4)-carba-

moyle, phénylcarbamoyle et adamantan-1-yle, dans lesquels le groupe phényle peut porter éventuellement de 1 à 4 substituants choisis parmi les groupes alkyle en C_1-C_4, halogéno, hydroxy, benzyloxy, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro et (alcoxy en C_1-C_4)-carbonyle, ou former avec le groupe -CH=C- adjacent et deux des atomes de carbone constituant le cycle A un groupe 1,2-dihydronaphtalène, 6,7-dihydro-5H-benzocycloheptène, 5,6,7,8-tétra-hydrocyclooctène, 4,5-dihydrobenzo[b]thiophène, 4,5-dihydroisobenzofurane, 7,8-dihydro-quinoline ou 7,8-dihydroisoquinoline pouvant être substitués par 1 à 3 substituants choisis parmi les (alkyle en C_1-C_4), halogéno, hydroxy, alkyloxy en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro, cyano et (alcoxy a C_1-C_4)-carbonyle; R^2 représente (i) un atome d'hydrogène, (ii) un groupe alkyle à chaîne linéaire ou ramifiée comportant de 1 à 11 atomes de carbone, alcényle en C_2-C_4 à chaîne linéaire ou ramifiée, alcynyle en C_2-C_4, cycloalkyle en C_3-C_7 monocyclique, bicyclo-[3,2,1]-oct-2-yle, bicyclo-[3,3,1]-nonan-2-yle, adamantan-1-yle, phényle ou naphtyle pouvant être substitués par 1 à 3 substituants choisis parmi les halogéno, nitro, nitrile, hydroxy, alcoxy en C_1-C_4, alkylthio en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, (alcoxy en C_1-C_4)-carbonyle, hydroxycarbonyle, (alkyle en C_1-C_6)-carbonyle, carbamoyle, mono- ou di-(alkyle en C_1-C_4)-carbamoyle, phényle, naphtyle, phénoxy, benzoyle, phénoxycarbonyle, phényl-(alkyle en C_1-C_4)-carbamoyle, phénylcarbamoyle et adamantan-1-yle, dans lesquels le groupe phényle peut porter éventuellement 1 à 4 substituants choisis parmi groupes alkyle en C_1-C_4, halogéno, hydroxy, benzyloxy, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro et (alcoxy en C_1-C_4)-carbonyle, ou (iii)(alkyle en C_1-C_6)-carbonyle, (cycloalkyle en C_3-C_8)-carbonyle, (cycloalkyle en C_3-C_8)-(alkyle en C_1-C_6)-carbonyle, (alcényl- ou alcycnyle en C_2-C_6)-carbonyle, benzoyle, naphtoyle, carbamoyle, mono- ou di-(alkyle en C_1-C_4)-carbamoyle, mono- ou di-(alcényle en C_3-C_6)-carbamoyle, phénylcarbamoyle, naphtylcarbamoyle, diphénylcarbamoyle, sulfonyle de sodium, alkylsulfonyle en C_1-C_6, (alcényle ou alcynyle en C_2-C_6)-sulfonyle, phénylsulfonyle, naphtalènesulfonyle, (alkyloxy en C_1-C_6)-carbonyle, (cycloalkyloxy en C_3-C_8)-carbonyle, cyclopentylméthyloxycarbonyle, (alcényle ou alcynyle en C_2-C_7)-oxycarbonyle, phényloxycarbonyle ou phényle-(alcoxy en C_1-C_2)-carbonyle, qui peut porter à son tour de 1 à 3 substituants choisis parmi les halogéno, nitro, nitrile, hydroxy, alcoxy en C_1-C_4, alkylthio en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, (alcoxy en C_1-C_4)-carbonyle, hydroxy carbonyle, (alkyle en C_1-C_6)-carbonyle, carbamoyle, mono- on di-(alkyle en C_1-C_4)-carbamoyle, phényle, naphtyle, phénoxy, benzoyle, phénoxycarbonyle, phényl-(alkyle en C_1-C_4)-carbamoyle, phénylcarbamoyle et adamantan-1-yle, dans lesquels le groupe phényle peut porter éventuellement de 1 à 4 substituants choisis parmi les groupes alkyle en C_1-C_4, halogéno, hydroxy, benzyloxy, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro et (alcoxy en C_1-C_4)-carbonyle, R^3 représente un groupe alkyle à chaîne linéaire ou ramifiée comportant de 1 à 11 atomes de carbone, alcényle à chaîne linéaire ou ramifiée en C_2-C_4, alcynyle en C_2-C_4, cycloalkyle en C_3-C_7 monocyclique, bicyclo-[3,2,1]-oct-2-yle, bicyclo-[3,3,1]-nonan-2-yle, adamantan-1-yle, phényle ou naphtyle pouvant être substitué par 1 à 3 substituants choisis parmi les halogéno, nitro, nitrile, hydroxy, alcoxy en C_1-C_4, alkylthio en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, (alcoxy en C_1-C_4)-carbonyle, hydroxycarbonyle, (alkyle en C_1-C_6)-carbonyle, carbamoyle, mono- ou di-(alkyle en C_1-C_4)-carbamoyle, phényle, naphtyle, phénoxy, benzoyle, phénoxycarbonyle, phényl-(alkyle en C_1-C_4)-carbamoyle, phénylcarbamoyle et adamantan-1-yle, dans lesquels le groupe phényle peut porter éventuellement de 1 à 4 substituants choisis parmi groupes alkyle en C_1-C_4, halogéno, hydroxy, benzyloxy, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro, et (alcoxy en C_1-C_4)-carbonyle, et n représente un nombre entier compris entre 2 et 6, ou un sel d'un tel composé.

2. Composé conforme à la revendication 1 dans lequel le cycle A est un benzène.

3. Composé conforme à la revendication 1 dans lequel le cycle A est un naphtalène ou anthracène.

4. Composé conforme à la revendication 1 dans lequel le cycle A est un membre du groupe constitué de thiophène, furane, pyrazole, thiazole, isothiazole, oxazole, isoxazole, imidazole, triazole, tétrazole, pyridine, pyrimidine et pyridazine.

5. Composé conforme à la revendication 1 dans lequel le cycle A est substitué on non par 1 à 3 substituants choisis dans le groupe des alkyle en C_1-C_4, halogéno, nitro, cyano, acétylamino, alcoxy en C_1-C_4, benzyle, benzoylamino, (alkyle en C_1-C_6)-sulfonyle, benzylsulfonyle, phénylsulfonylamino, benzylsulfonylamino, phénylcarbamoyle, méthoxycarbonyle et diéthoxycarbonyle.

6. Composé conforme à la revendication 1 dans lequel R^1 représente un atome d'hydrogène, un groupe alkyle en C_1-C_{11}, alcényle en C_2-C_4, alcynyle en C_2-C_4 ou cycloalkyle en C_3-C_7 monocyclique.

7. Composé conforme à la revendication 1 dans lequel R^1 forme avec le groupe adjacent -CH=CH- et deux atomes de carbone du cycle A un groupe 1,2-dihydronaphtalène.

8. Composé conforme à la revendication 7 dans lequel le groupe 1,2-dihydronaphtalène formé par le cycle à 5-7 chaînons et le cycle A est substitué ou non par 1 à 3 substituants choisis parmi les alkyle en C_1-C_4, halogéno, alcoxy en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro, cyano et (alcoxy en C_1-C_4)-carbonyle.

9. Composé conforme à la revendication 1 dans lequel R^2 représente un atome d'hydrogène, un groupe alkyle en C_1-C_{11}, alcényle en C_2-C_4, alcynyle en C_2-C_4 ou cycloalkyle en C_3-C_7 monocyclique.

10. Composé conforme à la revendication 1 dans lequel n est un nombre entier égal à 2, 3 ou 4.

11. Composé conforme à la revendication 1 dans lequel le cycle A est un résidu benzène, pyridine, furane ou thiophène pouvant être substitué par un alkyle en C_1-C_4, alcoxy en C_1-C_4, nitro, cyano, halogéno et/ou (alkyle en C_1-C_6)-sulfonyle, R^1 représente un atome d'hydrogène, un groupe alkyle en C_1-C_6 ou phényle, ou forme, avec le groupe adjacent -CH=CH- et deux atomes de carbone du cycle A, un groupe 1,2-dihydronaphtalène pouvant être substitué par un alcoxy en C_1-C_4, R^2 représente un atome d'hydrogène, un groupe alkyle en C_1-C_6 ou (alkyle en C_1-C_6)-carbonyle, R^3 représente un résidu benzyle et n est égal à 2.

12. Composé conforme à la revendication 1 dans lequel le cycle A représente un benzène, une pyridine, un furane ou un thiophène pouvant être substitué par un groupe alcoxy en C_1-C_4, R^1 est un atome d'hydrogène, un groupe alkyle en C_1-C_6 ou phényle ou forme, avec le groupe adjacent -CH=CH- et deux atomes de carbone du cycle A, un groupe 1,2-dihydronaphtalène pouvant être substitué par un alcoxy en C_1-C_4, R^2 représente un atome d'hydrogène, un groupe alkyle en C_1-C_6 ou (alkyle en C_1-C_6)-carbonyle, R^3 représente un groupe benzyle et n est égal à 2.

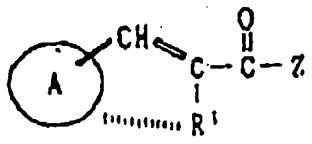
13. Composé conforme à la revendication 1 dans lequel le cycle A est un noyau benzène, R^1 est un atome d'hydrogène, R^2 est un atome d'hydrogène, un groupe alkyle en C_1-C_6 ou (alkyle en C_1-C_6)-carbonyle, R^3 est un résidu benzyle et n est égal à 2.

14. Composé conforme à la revendication 1 qui est le chlorhydrate de (E)-3-phényl-N-acétyle-N-[2-(1-benzylpipéridin-4-yl)-éthyl]-2-propénamide.

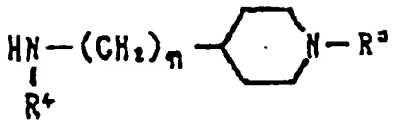
15. Composé conforme à la revendication 1 qui est le (E)-3-(pyrididyl)-N-[2-(1-benzylpipéridin-4-yl)-éthyl]-2-propénamide.

16. Composé conforme à la revendication 1 qui est le chlorhydrate de 3,4-dihydro-6,7-diméthoxy-N-[2-(1-benzylpipéridin-4-yl)-éthyl]-naphtalène-2-carboxamide.

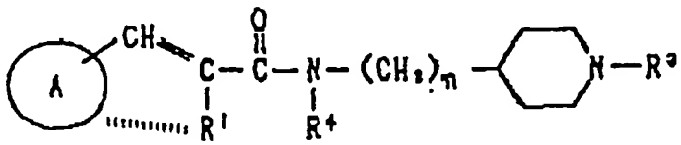
17. Procédé de préparation d'un composé conforme à la revendication 1, caractérisé en ce que
(A) l'on fait réagir un composé de formule :



dans lequel Z représente un groupe hydroxyle ou un groupe réactif d'un acide carboxylique, et les autres symboles ont la même signification que dans la revendication 1, avec un composé de formule :

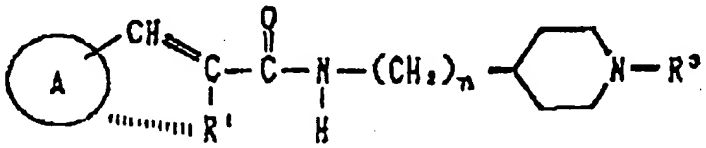


dans lequel R^4 représente un atome d'hydrogène ou un groupe alkyle à chaîne linéaire ou ramifiée comportant de 1 à 11 atomes de carbone, un groupe alcényle en C_2-C_4 à chaîne linéaire ou ramifiée, un groupe alcynyle en C_2-C_4, cycloalkyle en C_3-C_7 monocyclique, bicyclo[3,2,1]oct-2-yle, bicyclo-[3,3,1]-nonan-2-yle, adamantan-1-yle, phényle ou naphtyle pouvant être substitué par 1 à 3 substituants choisis parmi les halogéno, nitro, nitrile, hydroxy, alcoxy en C_1-C_4, alkylthio en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, (alcoxy en C_1-C_4)-carbonyle, hydroxycarbonyle, (alkyle en C_1-C_6)-carbonyle, carbamoyle, mono- ou di-(alkyle en C_1-C_4)-carbamoyle, phényle, naphtyle, phénoxy, benzoyle, phénoxycarbonyle, phényl-(alkyle en C_1-C_4)-carbamoyle, phénylcarbamoyle et adamantan-1-yle, dans lesquels le groupe phényle peut porter éventuellement de 1 à 4 substituants choisis parmi les groupes alkyle en C_1-C_4, halogéno, hydroxy, benzyloxy, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro et (alcoxy en C_1-C_4)-carbonyle, R^3 et n ont la même signification que celle définie dans la revendication 1 ou un sel d'un tel composé afin d'obtenir un dérivé amide d'un acide carboxylique insaturé représenté par la formule :

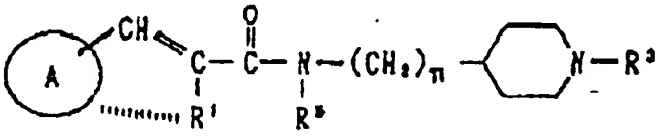


dans laquelle chaque symbol a la même signification que celle définie ci-dessus, ou un sel d'un tel composé,

(B) l'on soumet un composé de formule :

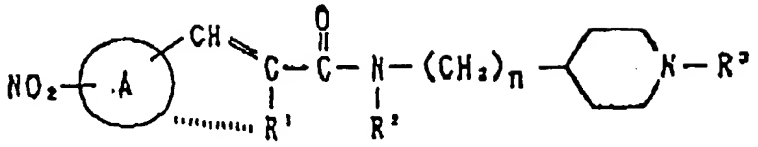


dans laquelle chaque symbole a la même signification que celle définie ci-dessus, à une réaction qui introduit un résidu hydrocarboné ou à une acylation pour obtenir un dérivé amide d'un acide carboxylique insaturé représenté par la formule :

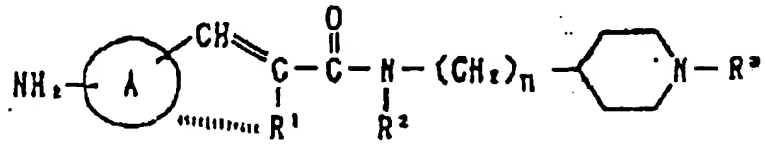


dans laquelle R^5 a la même signification que R^2 à l'exception de l'atome d'hydrogène, et les autres symboles ont la même signification que celle définie ci dessus, ou un sel d'un tel composé,

(C) l'on soumet un composé de formule :

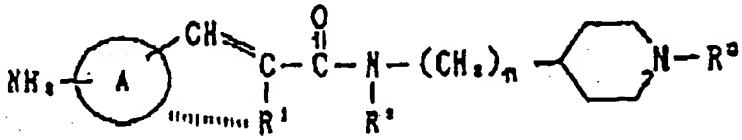


dans laquelle R^2 est celui défini dans la revendication 1, et les autres symboles ont la même signification que celle définie ci-dessus, ou un sel d'un tel composé, à une réduction afin d'obtenir un dérivé amide d'un acide carboxylique insaturé de formule :

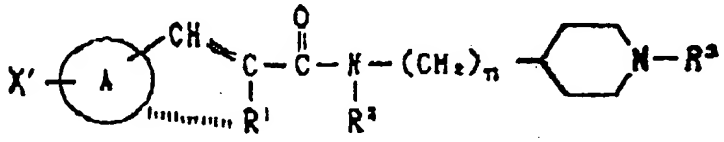


dans laquelle chaque symbole a la même signification que ci-dessus, ou un sel d'un tel composé, ou

(D) l'on soumet un composé de formule



dans laquelle chaque symbole a la même signification que ci-dessus, ou un sel d'un tel composé, à une acylation pour obtenir un dérivé amide d'un acide carboxylique insaturé de formule :



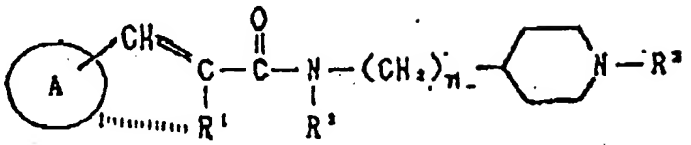
dans laquelle X' représente un groupe (alkyle en C_1-C_4)-carbonylamino ou (alkyle en C_1-C_4)-sulfonylamino, et les autres symboles ont la même signification que celle définie ci-dessus, ou un sel d'un tel composé.

18. Composition pharmaceutique contenant un composé conforme à la revendication 1 ensemble avec un véhicule ou un diluant de ce composé.

19. Utilisation d'un composé conforme à la revendication 1 comme composant dans la préparation d'un médicament pour améliorer les fonctions cérébrales d'un sujet atteint de démence sénile.

Revendications pour l'Etat contractant suivant : ES

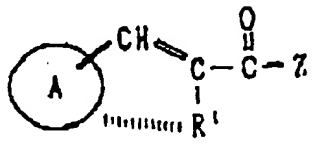
1. Procédé de préparation d'un composé de formule



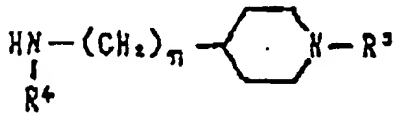
dans laquelle le cycle A représente un groupe benzène, naphtalène, anthracène ou un cycle hétérocyclique à 5 ou 6 chaînons comportant de 1 à 4 hétéroatomes choisis parmi l'azote, l'oxygène et le soufre, le cycle pouvant être substitué par 1 à 4 substituants choisis dans le groupe constitué des substituants alkyle en C_1-C_4, halogène, nitro, cyano, hydroxy, alcoxy en C_1-C_4, alkylthio en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, (alkyle en C_1-C_4)-carbonylamino, (alkyle en C_1-C_4)-sulfonylamino, (alkoxy en C_1-C_4)-carbonyle, hydroxycarbonyle, (alkyle en C_1-C_6)-carbonyle, carbamoyle, mono- ou di-(alkyle en C_1-C_4)-carbamoyle, (alkyle en C_1-C_6)-sulfonyle, phényle, phénoxy, benzoyle, phénoxycarbonyle, phényl-(alkyle en C_1-C_4)-carbamoyle, phénylcarbamoyle, phényl-(alkyle en C_1-C_4)-carbonylamino, benzoylamino, phényl-(alkyle en C_1-C_4)-sulfonyle, phénylsulfonyle, phényl-(alkyle en C_1-C_4)-sulfonylamino et phénylsulfonylamino, dans lesquels le groupe ou le motif phényle peut être à son tour substitué par un ou deux résidus choisis parmi les groupes alkyle en C_1-C_4, halogéno, hydroxy, benzyloxy, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro et (alcoxy en C_1-C_4)-carboxy, R^1 représente un atome d'hydrogène ou un groupe alkyle à chaîne linéaire ou ramifiée comportant de 1 à 11 atomes de carbone, alcényle en C_2-C_4 à chaîne ramifiée ou linéaire, alcynyle en C_2-C_4 cycloalkyle en C_3-C_7 monocyclique, bicyclo[3,2,1]oct-2-yle, bicyclo[3,3,1]nonan-2-yle, adamantan-1-yle, phényle ou naphtyle pouvant être substitué par 1 à 3 substituants choisis parmi les halogéno, nitro, nitrile, hydroxy, alcoxy en C_1-C_4, alkylthio en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, (alcoxy en C_1-C_4)-carbonyle, hydroxycarbonyle, (alkyle en C_1-C_6)-carbonyle, carbamoyle, mono- ou di-(alkyle en C_1-C_4)-carbamoyle, phényle, naphtyle, phénoxy, benzoyle, phénoxycarbonyle, phényl-(alkyle en C_1-C_4)-carbamoyle, phénylcarbamoyle et adamantan-1-yle, dans lesquels le groupe phényle peut porter éventuellement de 1 à 4 substituants choisis parmi les groupes alkyle en C_1-C_4, halogéno, hydroxy, benzyloxy, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro et (alcoxy en C_1-C_4)-carbonyle, ou former avec le groupe -CH=C- adjacent et deux des atomes de carbone constituant le cycle A un groupe 1,2-dihydronaphtalène, 6,7-dihydro-5H-benzocycloheptène, 5,6,7,8-tétra-hydrocyclooctène, 4,5-dihydrobenzo[b]thiophène, 4,5-dihydroisobenzofurane, 7,8-dihydro-quinoline ou 7,8-dihydroisoquinoline pouvant être substitués par 1 à 3 substituants choisis parmi les (alkyle en C_1-C_4), halogéno, hydroxy, alkyloxy en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro, cyano et (alcoxy en C_1-C_4)-carbonyle; R^2 représente (i) un atome d'hydrogène, (ii) un groupe alkyle à chaîne linéaire ou ramifiée comportant de 1 à 11 atomes de carbone, alcényle en C_2-C_4 à chaîne linéaire ou ramifiée, alcynyle en C_2-C_4, cycloalkyle en C_3-C_7 monocyclique, bicyclo-[3,2,1]-oct-2-yle, bicyclo-[3,3,1]-nonan-2-yle, adamantan-1-yle, phényle ou naphtyle pouvant être substitués par 1 à 3 substituants choisis parmi les halogéno, nitro, nitrile, hydroxy, alcoxy en C_1-C_4, alkylthio en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, (alcoxy en C_1-C_4)-carbonyle, hydroxycarbonyle, (alkyle en C_1-C_6)-carbonyle, carbamoyle, mono- ou di-(alkyle en C_1-C_4)-carbamoyle, phényle, naphtyle, phénoxy, benzoyle, phénoxycarbonyle, phényl-(alkyle en C_1-C_4)-carbamoyle, phénylcarbamoyle et adamantan-1-yle, dans lesquels le groupe phényle peut porter éventuellement 1 à 4 substituants choisis parmi groupes alkyle en C_1-C_4, halogéno, hydroxy, benzyloxy, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro et (alcoxy en C_1-C_4)-carbonyle, ou (iii)(alkyle en C_1-C_6)-carbonyle, (cycloalkyle en C_3-C_8)-carbonyle, (cycloalkyle en C_3-C_8)-(alkyle en C_1-C_6)-carbonyle, (alcényl- ou alcycnyle en C_2-C_6)-carbonyle, benzoyle, naphtoyle, carbamoyle, mono- ou di-(alkyle en C_1-C_4)-carbamoyle, mono- ou di-(alcényle en C_3-C_6)-carbamoyle, phénylcarbamoyle, naphtylcarbamoyle, diphénylcarbamoyle, sulfonyle de sodium, alkylsulfonyle en C_1-C_6, (alcényle ou alcynyle en C_2-C_6)-sulfonyle, phénylsulfonyle, naphtalènesulfonyle, (alkyloxy en C_1-C_6)-carbonyle, (cycloalkyloxy en C_3-C_8)-carbonyle, cyclopentylméthyloxycarbonyle, (alcényle ou alcynyle en C_2-C_7)-oxycarbonyle, phényloxycarbonyle ou phényle-(alcoxy en C_1-C_2)-carbonyle, qui peut porter à son tour de 1 à 3 substituants choisis parmi les halogéno, nitro, nitrile, hydroxy, alcoxy en C_1-C_4, alkylthio en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, (alcoxy en C_1-C_4)-carbonyle, hydroxy carbonyle, (alkyle en C_1-C_6)-carbonyle, carbamoyle, mono- ou di-(alkyle en C_1-C_4)-carbamoy-

le, phényle, naphtyle, phénoxy, benzoyle, phénoxycarbonyle, phényl-(alkyle en C_1-C_4)-carbamoyle, phénylcarbamoyle et adamantan-1-yle, dans lesquels le groupe phényle peut porter éventuellement de 1 à 4 substituants choisis parmi les groupes alkyle en C_1-C_4, halogéno, hydroxy, benzyloxy, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro et (alcoxy en C_1-C_4)-carbonyle, R^3 représente un groupe alkyle à chaîne linéaire ou ramifiée comportant de 1 à 11 atomes de carbone, alcényle à chaîne linéaire ou ramifiée en C_2-C_4, alcynyle en C_2-C_4, cycloalkyle en C_3-C_7 monocyclique, bicyclo-[3,2,1]-oct-2-yle, bicyclo-[3,3,1]-nonan-2-yle, adamantan-1-yle, phényle ou naphtyle pouvant être substitué par 1 à 3 substituants choisis parmi les halogéno, nitro, nitrile, hydroxy, alcoxy en C_1-C_4, alkylthio en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, (alcoxy en C_1-C_4)-carbonyle, hydroxycarbonyle, (alkyle en C_1-C_6)-carbonyle, carbamoyle, mono- ou di-(alkyle en C_1-C_4)-carbamoyle, phényle, naphtyle, phénoxy, benzoyle, phénoxycarbonyle, phényl-(alkyle en C_1-C_4)-carbamoyle, phénylcarbamoyle et adamantan-1-yle, dans lesquels le groupe phényle peut porter éventuellement de 1 à 4 substituants choisis parmi groupes alkyle en C_1-C_4, halogéno, hydroxy, benzyloxy, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro, et (alcoxy en C_1-C_4)-carbonyle, et n représente un nombre entier compris entre 2 et 6, ou un sel d'un tel composé, caractérisé en ce que

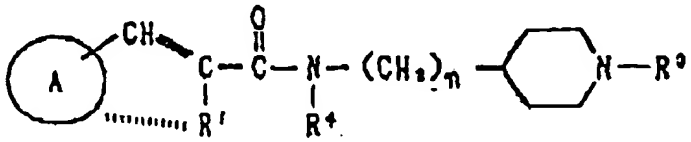
(A) l'on fait réagir un composé de formule :



dans lequel Z représente un groupe hydroxyle ou un groupe réactif d'un acide carboxylique, et les autres symboles ont la même signification que dans la revendication 1, avec un composé de formule :

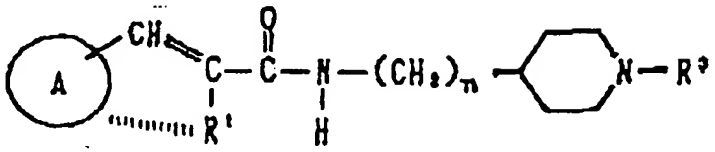


dans lequel R^4 représente un atome d'hydrogène ou un groupe alkyle à chaîne linéaire ou ramifiée comportant de 1 à 11 atomes de carbone, un groupe alcényle en C_2-C_4 à chaîne linéaire ou ramifiée, un groupe alcynyle en C_2-C_4, cycloalkyle en C_3-C_7 monocyclique, bicyclo[3,2,1]oct-2-yle, bicyclo-[3,3,1]-nonan-2-yle, adamantan-1-yle, phényle ou naphtyle pouvant être substitué par 1 à 3 substituants choisis parmi les halogéno, nitro, nitrile, hydroxy, alcoxy en C_1-C_4, alkylthio en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, (alcoxy en C_1-C_4)-carbonyle, hydroxycarbonyle, (alkyle en C_1-C_6)-carbonyle, carbamoyle, mono- ou di-(alkyle en C_1-C_4)-carbamoyle, phényle, naphtyle, phénoxy, benzoyle, phénoxycarbonyle, phényl-(alkyle en C_1-C_4)-carbamoyle, phénylcarbamoyle et adamantan-1-yle, dans lesquels le groupe phényle peut porter éventuellement de 1 à 4 substituants choisis parmi les groupes alkyle en C_1-C_4, halogéno, hydroxy, benzyloxy, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro et (alcoxy en C_1-C_4)-carbonyle, R^3 et n ont la même signification que celle définie dans la revendication 1 ou un sel d'un tel composé afin d'obtenir un dérivé amide d'un acide carboxylique insaturé représenté par la formule :

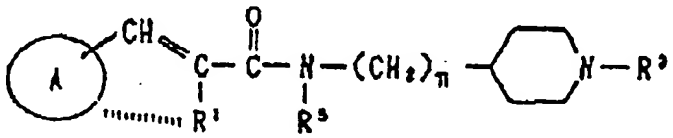


dans laquelle chaque symbole a la même signification que celle définie ci-dessus, ou un sel d'un tel

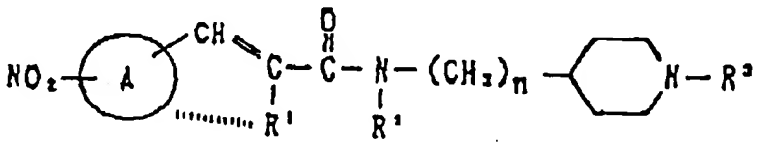
composé,
(B) l'on soumet un composé de formule :



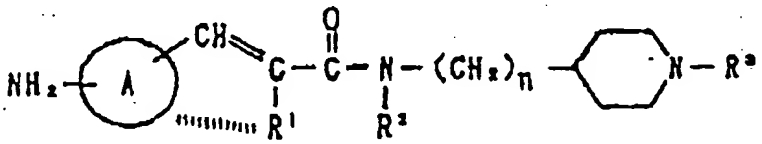
dans laquelle chaque symbole a la même signification que celle définie ci-dessus, à une réaction qui introduit un résidu hydrocarboné ou à une acylation pour obtenir un dérivé amide d'un acide carboxylique insaturé représenté par la formule :



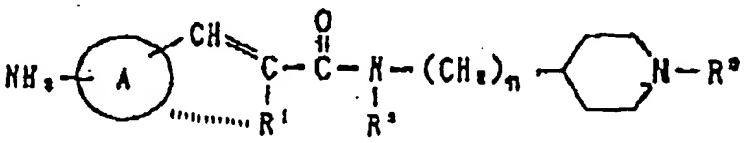
dans laquelle R^5 a la même signification que R^2 à l'exception de l'atome d'hydrogène, et les autres symboles ont la même signification que celle définie ci dessus, ou un sel d'un tel composé,
(C) l'on soumet un composé de formule :



dans laquelle R^2 est celui défini ci-dessus, et les autres symboles ont la même signification que celle définie ci-dessus, ou un sel d'un tel composé, à une réduction afin d'obtenir un dérivé amide d'un acide carboxylique insaturé de formule :

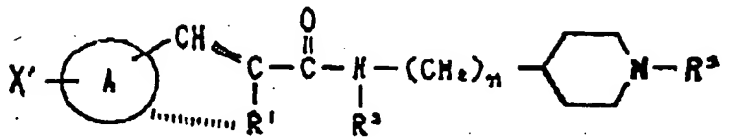


dans laquelle chaque symbole a la même signification que ci-dessus, ou un sel d'un tel composé, ou
(D) l'on soumet un composé de formule



dans laquelle chaque symbole a la même signification que ci-dessus, ou un sel d'un tel composé, à

une acylation pour obtenir un dérivé amide d'un acide carboxylique insaturé de formule :



dans laquelle X' représente un groupe (alkyle en C_1-C_4)-carbonylamino ou (alkyle en C_1-C_4)-sulfonylamino, et les autres symboles ont la même signification que celle définie ci-dessus, ou un sel d'un tel composé.

2. Procédé conforme à la revendication 1 dans lequel le cycle A est un benzène.

3. Procédé conforme à la revendication 1 dans lequel le cycle A est un naphtalène ou anthracène.

4. Procédé conforme à la revendication 1 dans lequel le cycle A est un membre du groupe constitué de thiophène, furane, pyrazole, thiazole, isothiazole, oxazole, isoxazole, imidazole, triazole, tétrazole, pyridine, pyrimidine et pyridazine.

5. Procédé conforme à la revendication 1 dans lequel le cycle A est substitué ou non par 1 à 3 substituants choisis dans le groupe des alkyle en C_1-C_4, halogéno, nitro, cyano, acétylamino, alcoxy en C_1-C_4, benzyle, benzoylamino, (alkyle en C_1-C_6)-sulfonyle, benzylsulfonyle, phénylsulfonylamino, benzylsulfonylamino, phénylcarbamoyle, méthoxycarbonyle et diéthoxycarbonyle.

6. Procédé conforme à la revendication 1 dans lequel R^1 représente un atome d'hydrogène, un groupe alkyle en C_1-C_{11}, alcényle en C_2-C_4, alcynyle en C_2-C_4 ou cycloalkyle en C_3-C_7 monocyclique.

7. Procédé conforme à la revendication 1 dans lequel R^1 forme avec le groupe adjacent -CH=CH- et deux atomes de carbone du cycle A un groupe 1,2-dihydronaphtalène.

8. Procédé conforme à la revendication 7 dans lequel le groupe 1,2-dihydronaphtalène formé par le cycle à 5-7 chaînons et le cycle A est substitué ou non par 1 à 3 substituants choisis parmi les alkyle en C_1-C_4, halogéno, alcoxy en C_1-C_4, amino, mono- ou di-(alkyle en C_1-C_4)-amino, nitro, cyano et (alcoxy en C_1-C_4)-carbonyle.

9. Procédé conforme à la revendication 1 dans lequel R^2 représente un atome d'hydrogène, un groupe alkyle en C_1-C_{11}, alcényle en C_2-C_4, alcynyle en C_2-C_4 ou cycloalkyle en C_3-C_7 monocyclique.

10. Procédé conforme à la revendication 1 dans lequel n est un nombre entier égal à 2, 3 ou 4.

11. Procédé conforme à la revendication 1 dans lequel le cycle A est un résidu benzène, pyridine, furane ou thiophène pouvant être substitué par un alkyle en C_1-C_4, alcoxy en C_1-C_4, nitro, cyano, halogéno et/ou (alkyle en C_1-C_6)-sulfonyle, R^1 représente un atome d'hydrogène, un groupe alkyle en C_1-C_6 ou phényle, ou forme, avec le groupe adjacent -CH=CH- et deux atomes de carbone du cycle A, un groupe 1,2-dihydronaphtalène pouvant être substitué par un alcoxy en C_1-C_4, R^2 représente un atome d'hydrogène, un groupe alkyle en C_1-C_6 ou (alkyle en C_1-C_6)-carbonyle, R^3 représente un résidu benzyle et n est égal à 2.

12. Procédé conforme à la revendication 1 dans lequel le cycle A représente un benzène, une pyridine, un furane ou un thiophène pouvant être substitué par un groupe alcoxy en C_1-C_4, R^1 est un atome d'hydrogène, un groupe alkyle en C_1-C_6 ou phényle ou forme, avec le groupe adjacent -CH=CH- et deux atomes de carbone du cycle A, un groupe 1,2-dihydronaphtalène pouvant être substitué par un alcoxy en C_1-C_4, R^2 représente un atome d'hydrogène, un groupe alkyle en C_1-C_6 ou (alkyle en C_1-C_6)-carbonyle, R^3 représente un groupe benzyle et n est égal à 2.

13. Procédé conforme à la revendication 1 dans lequel le cycle A est un noyau benzène, R^1 est un atome d'hydrogène, R^2 est un atome d'hydrogène, un groupe alkyle en C_1-C_6 ou (alkyle en C_1-C_6)-carbonyle, R^3 est un résidu benzyle et n est égal à 2.

14. Procédé conforme à la revendication 1 dans lequel le composé préparé est le chlorhydrate de (E)-3-phényl-N-acétyle-N-[2-(1-benzylpipéridin-4-yl)-éthyl]-2-propénamide.

15. Composé conforme à la revendication 1 dans lequel le composé préparé est le (E)-3-(pyrididyl)-N-[2-(1-benzylpipéridin-4-yl)-éthyl]-2-propénamide.

16. Procédé conforme à la revendication 1 dans lequel le composé préparé est le chlorhydrate de 3,4-dihydro-6,7-diméthoxy-N-[2-(1-benzylpipéridin-4-yl)-éthyl]-naphtalène-2-carboxamide.

17. Procédé de préparation d'une composition pharmaceutique contenant un composé préparé conformément aux revendications 1 à 16 ensemble avec un véhicule ou un diluant habituel de ce composé.

18. Procédé conforme à la revendication 17 pour la préparation d'un médicament pour améliorer les fonctions cérébrales d'un sujet atteint de démence sénile.